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Trifluralin (TREFLAN (Trade Name)), alpha,alpha,alpha - trifluoro -2,6 - dinitro - N,N - dipropyl - p - toluidine

(U.S.) Environmental Protection Agency
Washington, DC

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Trifluralin (TREFLAN®)

Position Document 4

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Treflan® Position Document 4

Special Pesticide Review Division,

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Executive Summary

On August 30, 1979, the Agency issued a preliminary notice of determination concerning the rebuttable presumption against registration (RPAR) of all pesticide products containing trifluralin (44 FR 50911). The Agency had determined that the trifluralin contaminant, N-nitroso-di-n-propylamine (NDPA) did meet or exceed the oncogenic risk criterion, thus necessitating an in-depth review to examine the risks and benefits associated with the use of products containing trifluralin.

In the Position Document (PD 1/2/3), the Agency proposed to cancel all registrations for products containing trifluralin unless registrants modified labeling of their products to reflect less than 1 ppm NDPA contamination. When the PD 1/2/3 was issued, the principal registrant, Elanco Products Co. (Elanco), had already instituted manufacturing methods to reduce the NDPA contamination level to less than 1 ppm NDPA.

The Agency also indicated in the PD 1/2/3 that the registrants would need to perform additional testing of trifluralin for reproductive effects, teratogenicity, and mutagenicity (including heritable spindle effects). The Agency specified that metabolism studies would need to be conducted on trifluralin containing NDPA to assess its ability to reach the mammalian gonad in a metabolically active form. Mutagenicity testing was also recommended for trifluralin's benzimidazole metabolites. At the time the PD 1/2/3 was issued Elanco was conducting a chronic feeding study to assess oncogenic effects due to administration of trifluralin with an NDPA concentration of less than 0.01 ppm, the limit of detection.

The Agency received comments on the Preliminary Notice of Determination and the PD 1/2/3 from the Secretary of the U.S. Department of Agriculture (USDA), the Scientific Advisory Panel (SAP), and 17 other interested parties. The USDA concurred with the Agency's proposed decision to continue registrations of products containing trifluralin with a limit of 1 ppm NDPA contamination.

The SAP agreed with the Agency's position and had specific recommendations for testing requirements. Further testing was recommended by the SAP for oncogenicity, mutagenic effects and spindle effects, using the product as currently produced with less than 1 ppm NDPA. The Elanco chronic feeding study submitted by Elanco fulfills the SAP's request for oncogenicity testing. The Agency agrees with the SAP about the need for further mutagenicity and spindle effects testing, but has not required the specific tests specified by the SAP. Instead, the Agency believes a better assessment of mutagenicity can be obtained by requiring further microbial tests, a dominant lethal test, and assessment for presence of active compounds in the mammalian gonad. Regarding testing for spindle effects, the Agency will identify outside scientists to help delineate a meaningful research program to assess risks from spindle inhibitors since current test systems are not adequate or sensitive enough.

When the appropriate tests have been identified the registrants will be required to identify any mutagenicity problem related to inhibition of spindle fiber formation or function. Lastly, the SAP questioned the need for mutagenicity testing of benzimidazoles, potential metabolites of trifluralin, as recommended in the PD 1/2/3. The Agency has determined that although benzimidazoles have been reported in *in vitro* studies, their presence in mammalian *in vivo* metabolism studies is uncertain, and, if present, the Agency assumes they probably exist in minute quantities. Therefore, the registrants will not be required to conduct mutagenicity studies on benzimidazole metabolites.

Of the seventeen other interested parties, eight concurred with the Agency's position, and six wanted more information, which was subsequently supplied by the Agency. Another had a question about worker exposure which is answered in the PD 4. Elanco Products Co. and American Cyanamid Co. commented in detail on the PD 1/2/3. Both submitted comments criticizing various aspects of the Agency's benefit analysis. The Agency has qualitatively reevaluated its analysis and finds it to be appropriate and reasonable. The Agency has determined that the benefits have not changed appreciably since the PD 1/2/3 was issued.

Elanco also submitted comments on the Agency's dietary and worker exposure and risk analysis; on the Agency's proposed requirements for additional reproduction, teratology, and mutagenicity studies; on the establishment of a maximum NDPA level in trifluralin containing products; and on the Agency's proposed label amendment. Elanco also submitted results of their trifluralin chronic feeding study, which indicated that high doses of trifluralin, with NDPA levels less than 0.01 ppm, are associated with a statistically significant increase in tumors of the kidney, bladder, and thyroid of rats when compared to controls. As a result of Elanco's comments and results from the chronic feeding study, the Agency has recalculated and reevaluated the dietary and worker exposure to nitrosamines and trifluralin and the risks associated with this exposure. The Agency has determined that the overall risk associated with exposure to Treflan® has not changed appreciably since the PD 1/2/3 was issued; the added risk due to exposure to trifluralin is offset by the reduction of NDPA by Elanco.

Because neither the risks nor the benefits have changed appreciably since the PD 1/2/3 was issued, the Agency has determined that the benefits still outweigh the risks if specific requirements are met. The Agency is currently requiring that all registrations for products containing trifluralin be allowed to continue only if the following requirements are met:

(1) Within 30 days after notification, registrants (present and future) must amend the inert ingredients statement in the Confidential Statement of Formula to reflect a total N-nitrosamine concentration of no greater than 0.5 ppm for technical trifluralin products. The inert ingredients

statement in the Confidential Statement of Formula of all formulated trifluralin products shall reflect a total N-nitrosamine contamination set as a function of the amount of trifluralin in the end use product. The total N-nitrosamine content in formulated products will be allowed to be twice what would normally be found in a straight-forward dilution. For example, a 25% formulated product could contain up to 0.25 ppm and a 50% formulated product could contain up to 0.50 ppm. This increase which can occur beyond a simple dilution of the technical material (containing an upper limit of 0.5 ppm) is to allow for possible nitrosamine generation to occur during the formulation process. The registrants must also advise the Agency that the level of total N-nitrosamine as stated in the Confidential Statement of Formulas is not exceeded.

(2) Registrants must perform mutagenicity testing on trifluralin (as stated in the PD 1/2/3; as well as testing for the presence of metabolically active product (trifluralin and NDPA) in the mammalian gonad as well as germinal testing.

(3) Registrants must perform testing of trifluralin for reproductive and teratogenic effects, since there are not adequate data to assess risks due to trifluralin in these areas.

(4) Registrants must conduct a field monitoring study to assess potential toxic effects to aquatic organisms, since, in light of new data and a reevaluation of existing information, the Agency determined that trifluralin could reach aquatic environments through soil runoff and, because of bioconcentration abilities, could be harmful to fish and molluscs.

An economic analysis concerning the cost of the data requirements was conducted. The estimation of the total cost of the required data and the estimated value of future trifluralin earnings indicate that it is economically feasible for the registrants to develop the data required for continued registration.

I. Introduction

Section 12(a)(1)(A) of the Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA, (7 U.S.C. 136 et seq.) prohibits the sale or distribution of pesticide products which are not registered by the EPA Administrator, and Section 3 of the Act sets forth the registration procedures. Before a pesticide may be registered, however, the Administrator must determine that its use will not result in "unreasonable adverse effects on the environment," [Sec. 3(c)(5)(C)], defined in Section 2(bb) of FIFRA as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide." Therefore, any decision on pesticide registration must take into account both the risks and the benefits associated with the pesticide's use.

Under Section 6(b) of FIFRA, the Administrator may issue a notice of intent to cancel the registration of a pesticide or to change its classification if it appears that the pesticide or its labeling "does not comply with the provisions of (FIFRA) or, when used in accordance with widespread and commonly recognized practice, generally causes unreasonable adverse effects on the environment." Thus, the Administrator may cancel the registration of a pesticide that no longer satisfies the statutory standard for registration. The Administrator may also change the classification of any use of a pesticide if he determines that such a change "is necessary to prevent unreasonable adverse effects on the environment" (FIFRA 3(d)(2)).

To implement its authorized functions, the Agency designed the Rebuttable Presumption Against Registration (RPAR) process to gather data on the risks and benefits associated with the uses of suspect pesticides. By allowing all interested parties to participate by submitting information, this process enables EPA to make balanced decisions concerning problem pesticides. The RPAR process is set forth in 40 CFR 162.11 which describes various risk criteria and provides that an RPAR shall arise if the Agency determines that any of these criteria has been met or exceeded.

Once a rebuttable presumption has arisen, registrants, applicants, and interested persons may submit evidence in rebuttal, or in support, of the presumption. These parties may also submit evidence on the economic, social, and environmental benefits of any use of the pesticide. If the presumptions of risk are not rebutted, the evidence pertaining to benefits must be evaluated and considered together with the evidence pertaining to risk. Various risk-reduction measures and their costs are analyzed. The Agency then determines whether the pesticide may be regulated so that a balance is achieved between risks and benefits. If the statutory balance cannot be reached for any given use, the registrations for that use must be cancelled.

On August 30, 1979, the Agency issued a preliminary notice of determination concerning the rebuttable presumption against registration and the continued registration of all pesticide products containing trifluralin (Treflan® EC, registered trademark) (44 FR 50911). The trifluralin RPAR review differed somewhat from the typical RPAR review in that two of the analytical RPAR phases (the initial determination that the risk criteria had been exceeded and the weighing of risks and benefits to determine the appropriate regulatory action) were combined. The Position Document (PD) 1/2/3 presented a detailed description of this RPAR review and proposed a decision to conclude the RPAR process. The PD 1/2/3 did not accompany the Notice, but copies were provided to all registrants and any other concerned parties.

In that Position Document the Agency proposed to cancel all registrations for products containing trifluralin unless registrants modifed labeling of their products to reflect less than 1 ppm N-nitrosodipropylamine (NDPA) contamination. The principal registrant, Elanco Products Company (Elanco), had already reduced the NDPA contamination to less than 1 ppm when the PD 1/2/3 was issued. This requirement was intended to pertain to both the product label and the confidential statement of formula maintained by the Agency. In addition, the Agency indicated that registrants of trifluralin containing products would have to do the following: certify this level to be the upper limit of contamination, advise the Agency of quality control procedures instituted to assure that the level of NDPA did not exceed 1 ppm, and maintain accurate quality control records on these products.

The Agency indicated that the registrants would be required to submit the results of the ongoing oncogenicity study, and to perform additional testing of trifluralin for reproductive effects, teratogenicity, and mutagenicity (including heritable spindle effects). The Agency also stated that mutagenicity testing was required on the benzimidazole metabolites of trifluralin and that metabolism studies were required on trifluralin with NDPA in order to assess the ability of trifluralin and/or NDPA to reach the mammalian gonad in a metabolically active form.

Sections 6(b) and 25(d) of FIFRA require that the Agency submit notices of the proposed decision to the Secretary of the U.S. Department of Agriculture (USDA) for comment on the impact of the proposed action on the agricultural economy and to the FIFRA Scientific Advisory Panel (SAP) for comment on the impact of the proposed action on health and the environment. In accordance with FIFRA, the Secretary and the SAP were invited to comment in writing within 30 days of receiving the notice. The Agency is required to publish their written comments, if submitted within 30 days of the receipt of the Notice, and the EPA Administrator's response to these comments.

Although not required to do so under the statute, the Agency decided that it was consistent with the purposes of the RPAR process and the Agency's overall policy of open decisionmaking to also afford registrants and other interested persons an opportunity to comment on the basis for the proposed action while it was under review by the Secretary of Agriculture and the SAP. The Position Document 1/2/3 was therefore made available to all interested parties for comment.

Since the preliminary notice of determination and notice of availability of the PD 1/2/3 was published on August 30, 1979, the Agency has received new information and a number of comments from interested parties. The new information, including the results of a chronic feeding study submitted by Elanco, resulted in revisions in the exposure and risk analyses; this is presented in detail in Section II of this document. Responses from the SAP, the USDA, and other interested parties have been analyzed and are addressed in Section III of this document. Section IV summarizes the Agency's decision concerning pesticide products containing trifluralin. The regulatory position takes into account all comments from the SAP, USDA, and other interested parties and is a slight modification of "option 3" set forth in the PD 1/2/3. Because the new information did not necessitate a change in this regulatory position, the Agency determined that it was not necessary to have the SAP review the study.

The responses from the SAP and the USDA are presented in their entirety in Appendix A and Appendix B, respectively. Appendix C contains exposure data on Treflan® from the Agency (Mittelman,1978) which was incorporated in the calculations for estimating current exposure to trifluralin and nitrosamines. Appendix C, and Appendix D which contains the PD 1/2/3, are available on request. All comments are available for review in the public file in the office of the Document Control Officer, Chemical Information Division, Room E 477, (TS-793), EPA, 401 M Street, S.W.; Washington, D.C; 20460.

II. New Information and Revisions to the PD 1/2/3

A. Elanco's Chronic Feeding Study

In the trifluralin Position Document 1/2/3, the Agency mentioned that tests were being performed by the principal trifluralin registrant, Elanco, to determine the oncogenicity of trifluralin in which the level of NDPA contamination was below the limits of detection. These tests were completed and the results were submitted to the Agency in September, 1980. Studies were conducted on two rodent species: B6C3F1 mice and Fischer 344 rats (Elanco, 1980d). The test substance, purified trifluralin containing NDPA at levels below the 0.01 ppm analytical detection limit, was administered in the diet over a period of two years. At the end of the study period the survivors were sacrificed and pathological examinations were made of each animal in the study. Hematology and blood chemistry tests were also performed.

In the mouse study, a total of 720 animals were tested, using a control group of 120 males and 120 females, and three treatment groups of 80 males and 80 females each. The diets of the treatment groups contained trifluralin in proportions of 563 ppm, 2250 ppm and 4500 ppm respectively. Elanco scientists concluded that the "primary effects of treatment...were reduced body weight and manifestations of renal toxicity", and that "there was no evidence that treatment induced increases of benign or malignant neoplasms" (Elanco 1980d). The Agency considers this mouse study to be valid, and agrees with Elanco that the results of the study do not show evidence of oncogenicity for trifluralin in B6C3F1 mice (Kasza, 1981; Chen and Haberman, 1981).

In the rat study a total of 480 rats were distributed among a control group and three treatment groups, each group containing 60 males and 60 females. Rats in the treatment groups were fed diets containing 813 ppm, 3250 ppm and 6500 ppm of trifluralin respectively. Elanco found that the only significant increase in malignant neoplasms occurred in the kidneys of male rats at all doses; the incidences were dose-related. An increase in benign bladder neoplasms was also noted by Elanco in all dose groups, an increase which was significant and dose-related for female rats, and for male and female rats considered together, but was not significant for male rats alone. A slight increase in benign interstitial cell tumors of the testes was found, in all dose groups; these increases were not reported to be statistically significant. Elanco scientists also noted a high incidence of chronic renal disease and the presence of renal calculi. Elanco reported the presence of chronic renal disease, characterized as progressive glomerulonephrosis, as being significant for the two highest dose groups. Renal calculi were also found in a high proportion of rats in all treatment groups; the incidence of renal calculi was dose-related. The incidence of renal calculi in the highest dose group was 42 out of 60 male and 42 out of 60 females.

Elanco does not interpret the increase in kidney and bladder neoplasms to be evidence of the oncogenicity of trifluralin. Elanco states that the fact that both urinary tract tumors and renal calculi were found in this study, but not in previous rat studies, indicates that the test compound, trifluralin, was not directly responsible for the excess tumors, and that other causal factors may have been present (Elanco, 1980d; Elanco 1980e). In particular, Elanco implicates the presence of renal calculi as a potential cause of the tumors. Renal calculi, described as "small mineral deposits in the renal pelvis epithelium and/or the calices" (Elanco, 1980d) and characterized as "similar to kidney stones" (Elanco, 1980e), were found in a high proportion of test animals. Since renal calculi have been shown to cause mechanical damage leading to neoplastic changes like those observed in the study, Elanco postulates that the excess tumors may have resulted from the presence of the calculi, or some interaction between the test substance and calculi. Elanco concludes that the results of the rat chronic feeding study do not permit a conclusive evaluation of the oncogenicity of trifluralin, since the presence of renal calculi provides an alternate explanation for the formation of the urinary tract tumors. Elanco scientists also suggest that the neoplastic response in the urinary tract seen in this study may be related to traits peculiar to Fischer 344 rats, since studies with trifluralin using other strains did not result in similar findings.

Agency scientists have reviewed the Elanco rat study and have found it to be a valid test for the oncogenicity of trifluralin (Kasza, 1981; Chen and Haberman, 1981; Barton, 1981). The Agency has arrived at a different interpretation of the results, however, regarding the types and significance of tumors showing increases in frequency as a result of treatment with trifluralin. Significant increases were found by Agency scientists in two types of tumors: tumors of the urinary (bladder and kidney) transitional epithelium in both male and female rats and follicular tumors of the thyroid in male rats (Chen and Haberman, 1981; Barton, 1981). Information on the incidence of these tumors is summarized in Table 1 (Haberman, 1981; Chen and Haberman, 1981).

In its analysis of the reported incidence of urinary tract tumors, the Agency considers that bladder papillomas, bladder carcinomas and renal pelvis carcinomas should be counted together, since they are similar tumors of a continuous epithelial tissue found in both the bladder and renal pelvis and exposed to the same substances in formation of the urine (Kasza, 1981). These neoplasms have been grouped together as tumors of the urinary transitional epithelium (Kasza, 1981; Chen and Haberman, 1981; Barton, 1981). In male rats, there were such tumors in 3 of 60 low dose animals, 3 of 60 in the middle dose group, and 6 of 60 at the highest dose. Compared to an absence of such tumors in 60 control animals, this increase is significant for the high dose at a value of $p = 0.014$ by the Fisher exact test. For female rats, no urinary tract tumors were found in the low dose groups of 60 animals each, but 1 tumor was found in the middle dose group and 5 tumors were found in the high dose group. Compared to the absence of such tumors in the 60 control animals, this increase at the high dose level is significant at a value of $p = 0.029$ by the Fisher exact test.

The Agency differs with Elanco about the significance of the presence of renal calculi in many of the treated animals. There are basically three aspects of the chronic feeding study results which, in the judgement of Agency scientists,

Table 1

Tumor Incidence[a] in Rats in the Elanco Chronic Feeding Study of Trifluralin[b]

Tumor Type and Site	Sex	Dose (in ppm)				Statistical Significance
		0	813	3250	6500	(Fisher Exact Test) (High Dose vs. Control)
Transitional Cell Papilloma and Carcinoma (Kidney and Bladder)	Male	0/60	3/60	3/60	6/60	0.014
	Female	0/60	0/60	1/60	5/60	0.029
Follicular Adenoma and Carcinoma (Thyroid Gland)	Male[d]	5/60	2/60	8/60	13/60	0.036[e]
Combined Tumors[c] (Kidney, Bladder and/or Thyroid)	Male[d]	5/60	5/60	9/60	17/60	0.004

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[a] Number of animals with tumors/number of animals in treatment or control group.

[b] Haberman, 1981.

[c] Each rat had at least one tumor.

[d] Increase in tumor incidence is significant for males only.

[e] Dose response is significant at a level $p < 0.01$ when computed by the Cochran-Armitage Test.

are not consistent with Elanco's conclusions that the presence of renal calculi are likely to have produced the observed increase in urinary tract tumors. First, the tumors are found in both the bladder and renal pelvis, but calculi were not observed in the bladder in this study. Since the mechanism proposed by Elanco is a progression from the formation of calculi to hyperplasia, then to neoplasia, such a mechanism would not explain the occurrence of tumors in the bladder, where no calculi were found (Kasza, 1981).

Second, "the 'calculi' reported in the renal pelvis were microscopic calcifications rather than stones. Evidence in the literature provides substantial confirmation of the concept that stones can cause tumors of the urinary tract in rats. The evidence that crystals or microscopic calcifications can cause urinary tract tumors in rats or in humans is more equivocal." (Kasza, 1981). Since stones and microscopic calcifications differ in their tumor-causing ability, Agency scientists do not consider the studies cited by Elanco concerning stones to be directly relevant to the question of the tumorigenicity of the microscopic calcifications found in the present study.

Third, if calcification, hyperplasia and neoplasia are sequential stages in the development of tumors, a correlation between the dose-response curves for each of those conditons would be expected. However, the dose-response curves for calcifications, hyperplasia and neoplasia "do not show consistent correlations" (Kasza, 1981).

In view of these serious inconsistencies between the experimental results and Elanco's proposed mechanism for oncogenicity, the Agency has concluded that Elanco has not established the role of the observed micro-calcifications in the formation of urinary tract tumors with sufficient certainty for the Agency to alter its conclusion that trifluralin treatment is associated with the production of kidney and bladder tumors in rats.

The Agency also finds significant evidence of an increased incidence of tumors of the follicular epithelium of the thyroid in male rats (Chen and Haberman, 1981; Barton, 1981). The Elanco study found five different tumor types in the follicular epithelium: follicular adenoma, follicular papillary adenoma, follicular cystadenoma, papillary crystadenoma, and follicular carcinoma. The Agency does not consider these lesions to be different tumors for the purpose of oncogenicity testing of a pesticide, since they occur in a single cell type and are differentiated only by having cystic or papillary components (Kasza, 1981). In male rats, thyroid follicular epithelial tumors were found in 2 of 60 low dose animals, 8 of 60 at the middle dose, and 13 of 60 at the high dose. Compared to an incidence of 5 tumors in 60 control animals, the results in the high dose group are significant at $p=0.036$ by the Fisher exact test, and significantly dose-related at $p<0.01$ by the Cochran-Armitage trend test. No significant increase or dose-related trend was found in female rats. The Agency concludes that trifluralin treatment is also associated with the production of thyroid tumors in male rats.

B. Revised Exposure Estimates

In addition to the chronic feeding study, other information has come to the Agency's attention since 1979 which results in changes in or amendments to the exposure estimates presented in the PD 1/2/3.

Trifluralin itself has been shown to be associated with tumor production in laboratory animals. Therefore, it became necessary for the Agency to estimate dietary exposure to the general population and to estimate exposure to mixer/applicator/loaders and also to workers reentering fields treated with trifluralin. The PD 1/2/3 had only addressed exposure and risk associated with NDPA.

The Agency also received further information on the nitrosamine contamination in Treflan® EC. The NDPA exposure estimates in the PD 1/2/3 were based on a contamination of 5 ppm. However, since that time Elanco has altered the procedures in the manufacturing process and has reduced this level of contamination. Elanco (1980a, 1980b) reported the results of 635 analyses of Treflan® EC for both NDPA and total nitrosamine contamination. The samples, representing production runs from September 1, 1979, to May 30, 1980, were found to contain average NDPA residues of 0.10 ppm (0.00 to 0.962) and an average of 0.12 ppm for total nitrosamine residues (0.00 to 0.96). The total nitrosamine residues included both NDPA (C_6) and other nitrosamines identified as having either seven or eight carbon atoms. These will be referred to as C_7/C_8 nitrosamines in this document and are assumed to be present at an average level of 0.02 ppm. This figure was obtained by substracting the average NDPA contamination of 0.10 ppm from the average total nitrosamine contamination of 0.12 ppm (Regelman, 1981a). Quality control in the manufacture of Treflan® EC is expected to maintain nitrosamine impurities at less than 1 ppm. Elanco (1981) has identified the chemical structure of the C_7 nitrosamine and has partially identified that of the C_8 nitrosamine; this information is classified as confidential, however, and will not be presented in this document.

Since 1979 when the PD 1/2/3 was issued, Treflan® EC has been registered for weed control in barley and grain sorghum. Dietary exposures for these two crops have been estimated and have been included in Table 2 which presents estimates for exposure to trifluralin, NDPA, and C_7/C_8 nitrosamines. Worker exposures for these two crops could not be calculated because information on the hours spent by the workers during application, mixing and loading, and during reentry activities is not readily available. As shown in Table 2, the increase in dietary exposure for barley and sorghum is extremely small. Based on exposure estimates from other uses, it is reasonable to assume there would be an extremely small increase in worker exposure as well.

1. Dietary Exposure

In the PD 1/2/3, the dietary exposure estimates for NDPA were based on tolerances for trifluralin. The risk from the dietary exposure to NDPA was stated to be a maximum number based on the assumption that trifluralin residues were present in concentrations equal to their established tolerances which ranged from 0.05 to 2.00 ppm. It was stated in the PD 1/2/3 (p.81) that NDPA residues were probably much lower than those estimated.

Because new data indicated that there could be risk associated with trifluralin itself (Elanco, 1980d) and the C_7/C_8 nitrosamines as well (Elanco, 1978a), the Agency decided to base the new dietary estimate on studies which measured actual residues of trifluralin in order to obtain a more accurate estimate of dietary exposure. These studies had been submitted by Elanco in support of petitions for tolerances for the many food commodities treated with Treflan®. In using the residue data (summarized by Regelman, 1981a), the Agency is assuming that the studies are representative of "real world" conditions and that, therefore, the exposure estimate based on these data will reflect more accurately the actual dietary exposure to trifluralin and, thus, NDPA, and C_7/C_8 nitrosamines.

This dietary estimate will include, therefore, potential exposure to trifluralin, NDPA, and C_7/C_8 nitrosamine residues in Treflan® EC-treated crops, since the risk is associated with the active ingredient as well as with the various nitrosamine impurities.

All petitions for tolerances which had previously been submitted to the Agency were reviewed and virtually all reported residues of trifluralin were either at or below the limit of detection of the method used (0.01 ppm). The reported residues (Table 2) are approximately one fifth of the established tolerances. Assuming the data to be representative of treated crops generally, the Agency assigned a value of 0.01 ppm trifluralin to all food commodities in which NDR (no detectable residues) or <0.01 ppm were reported. It is reasonable to assume that actual residues of trifluralin are at or below this level.

Residues were found in some of the food commodities studied, but most were below the limit of detection. Only in carrots, peppermint oil and spearmint oil were residues consistently found above the limit of detection. In carrots, residues ranged from 0.49 to 0.86 ppm. Elanco observed that these residues were not uniformly distributed throughout the carrot, concentrating mostly within the outer 1/16 inch (74 percent). Assuming that washing or peeling of the outer skin would reduce exposure to trifluralin below 0.86 ppm the Agency used an average value of 0.65 ppm in the dietary estimate. In both peppermint oil and spearmint oil, residues ranged from 0.57 to 1.71 ppm. Since residues could routinely be present at these levels the Agency chose to use the tolerance level of 2.00 ppm in the dietary estimate.

Table 2

Dietary Exposure to Trifluralin, NDPA and C_7/C_8 Nitrosamines

Commodity	Trifluralin Residues[a] (ppm)	Fraction		Daily Intake (mg/kg diet)		
		of Food in Diet	of Crop Treated	Trifluralin ($x10^{-6}$)	NDPA[c] ($x10^{-12}$)	C_7/C_8[d] ($x10^{-12}$)
Asparagus	<0.01	.0014	1.000	14.00	3.15	0.63
Barley	<0.01	.0007	0.030[e]	0.21	0.05	0.01
Carrots	0.65[f]	.0048	0.403	1257.36	282.55	56.51
Citrus Fruit	<0.01	.0381	0.079	30.10	6.76	1.35
Corn, grain	<0.01	.0100	1.000	100.00	22.47	4.49
Cottonseed	<0.01	.0015	0.695	10.43	2.34	0.47
Cucurbits, Cantaloupe	<0.01	.0052	0.100	5.20	1.17	0.23
Cucumber	<0.01	.0073	0.291	21.24	4.77	0.95
Watermelon	<0.01	.0143	0.300	42.90	9.64	1.93
Dill	<0.01	.0003	0.536	1.61	0.36	0.07
Fruiting Vegetables, Green Peppers	<0.01	.0012	0.378	4.54	1.02	0.20
Tomatoes	<0.01	.0287	0.688	197.46	44.37	8.87
Grapes/Raisins	<0.01	.0049	0.079	3.87	0.87	0.17
Hops	<0.01	.0003	0.251	0.75	0.17	0.03
Leafy Vegetables, Broccoli	<0.01	.0010	0.650	6.50	1.46	0.29
Brussel Sprouts	<0.01	.0003	0.650	1.95	0.44	0.09
Cabbage	<0.01	.0074	0.665	49.21	11.06	2.21
Cauliflower	<0.01	.0007	0.546	3.82	0.86	0.17
Celery	<0.01	.0029	0.394	11.43	2.57	0.51
Collard	<0.01	.0008	0.960	7.68	1.73	0.35
Kale	<0.01	.0003	0.960	2.88	0.65	0.13
Mustard Greens	<0.01	.0006	0.859	5.15	1.16	0.23
Turnip Greens	<0.01	.0003	0.963	2.89	0.65	0.13
Others	<0.01	.0133	1.000	133.00	29.89	5.98
Mung Beans (canned sprouts)	<0.01	.0003	1.000	3.00	0.67	0.13
Mustard Seed	<0.01	.0003	1.000	3.00	0.67	0.13
Nuts	<0.01	.0010	0.079	0.79	0.18	0.04
Okra	<0.01	.0007	1.000	7.00	1.57	0.31
Peanuts	<0.01	.0036	0.196	7.06	1.59	0.32
Peppermint Oil	2.00[g]	.0003	0.077	46.20	10.38	2.08
Root Crop Vegetables, Potatoes	<0.01	.0543	0.053	28.78	6.47	1.29
Others	<0.01	.0554	1.000	554.00	124.49	24.90
Safflower Seeds	<0.01	.0003	1.000	3.00	0.67	0.13

Table 2 (continued)

Dietary Exposure to Trifluralin, NDPA and C_7/C_8 Nitrosamines

Commodity		Trifluralin Residues[a] (ppm)	Fraction		Daily Intake (mg/kg diet)		
			of Food in Diet	of Crop Treated	Trifluralin ($x10^{-6}$)	NDPA[c] ($x10^{-12}$)	C_7/C_8[d] ($x10^{-12}$)
Seed/Pod Vegetables,	Beans	<0.01	.0204	0.756	154.22	34.66	6.93
	Soybeans	<0.01	.0092	0.377	34.68	7.79	1.56
	Peas	<0.01	.0069	0.138	9.52	2.14	0.43
Sorghum, grain		<0.01	.0003	0.020[e]	0.06	0.01	0.00
Spearmint Oil		2.00[g]	.0003	0.077	46.20	10.38	2.08
Stone Fruits		<0.01	.0125	1.000	125.00	28.09	5.62
Sugar, Cane & Beet		<0.01	.0364	0.117	42.59	9.57	1.91
Sunflower Seeds		<0.01	.0003	0.650	1.95	0.44	0.09
Wheat Grain and Straw		<0.01	.1036	0.011	11.40	2.56	0.51
TOTALS					2992.62	672.50	134.50

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a/ Regelman, 1981a.

b/ Assumes that NDPA levels continue to remain <0.10 ppm in Treflan EC, that C_7/C_8 levels continue to remain <0.02 ppm in Treflan EC, and that current usage does not increase.

Daily Intake (Trifluralin) = Trifluralin Residues x Fraction of Food in Diet x Fraction of Crop Treated

c/ The ratio of trifluralin to NDPA in Treflan EC (44.5% trifluralin) is assumed to be 4,450,000:1 (445,000 ppm:0.10 ppm). Daily Intake (NDPA) = Daily Intake (trifluralin) ÷ 4,450,000

d/ The ratio of trifluralin to C_7/C_8 nitrosamines in Treflan EC (44.5% trifluralin) is assumed to be 22,250,000:1 (445,000 ppm:0.02 ppm).
Daily Intake (C_7/C_8) = Daily Intake (trifluralin) ÷ 22,250,000

e/ Langley, C., 1981.

f/ Residues ranged from 0.49-0.86 ppm.

g/ Residues were assumed to be present at the tolerance level.

For purposes of this dietary estimate, the Agency assumed that NDPA was present in Treflan® EC at a level of 0.10 ppm (in contrast to the 5.0 ppm level assumed in the PD 1/2/3), and that all other nitrosamine impurities (C_7/C_8) were present at a level of 0.02 ppm.

Treflan® EC contains 44.5 percent trifluralin or 445,000 ppm. At the levels of 0.10 ppm and 0.02 ppm in Treflan® EC, the ratio of trifluralin to NDPA and to the C_7/C_8 nitrosamine contaminants would be 4,450,000 : 1 and 22,250,000 : 1, respectively (445,000 : 0.10 and 445,000: 0.02). The Agency used these ratios to estimate exposure to nitrosamines based on trifluralin residue data. In order to estimate possible exposure to other levels of nitrosamine contamination, one could adjust these ratios appropriately.

Trifluralin is recoverable utilizing the FDA market basket survey procedures but no such residues have been reported. There are a few FDA reports of trifluralin found by its surveillance and compliance programs, for the period 1975-1979 (USEPA, 1979, and FDA, 1981). No residues were found in surveys by the Animal and Plant Health Inspection Service (APHIS) of USDA. Furthermore, there are no known reports of residues of nitrosamines found in any of these surveys. However, since there are no tolerances for nitrosamines, these surveys would not normally analyze for such impurities.

For these reasons, the Agency used the following information to estimate potential dietary exposure to trifluralin, NDPA and C_7/C_8 nitrosamines (Regelman, 1981a).

- o the percentage of crop acreage treated;
- o actual trifluralin residue data;
- o food factors;
- o estimated trifluralin to nitrosamine ratios (noted above).

Where trifluralin results were reported as NDR (no detectable residues) at the limit of detection of 0.005 to 0.01 ppm, or as <0.01 ppm, the Agency assumed that residues were present at the 0.01 ppm limit of detection. Table 2 summarizes these data.

Assuming a dietary intake of 1.5 kg per day, the dietary exposures (Table 2) for trifluralin range from 0.06×10^{-6} mg/kg diet/day for sorghum to 1257.36×10^{-6} mg/kg diet/day for carrots; for NDPA from 0.01×10^{-12} mg/kg diet/day for sorghum to 282×10^{-12} mg/kg diet/day for carrots; for C_7/C_8 nitrosamines from zero for sorghum to 56.51×10^{-12} for carrots. Using a dietary intake of 1.5 kg/day and a body weight of 65 kg, the total dietary exposure to trifluralin, NDPA and C_7/C_8 nitrosamines was calculated to be 69.06×10^{-6}, 15.52×10^{-12} and 3.10×10^{-12} mg/kg body weight/day, respectively. (These values were calculated by multiplying the total daily intakes shown in Table 2 by 1.5 and then dividing by 65.)

In the Treflan® PD 1/2/3, total dietary exposure to trifluralin was not included (since no RPAR criterion had been met at that time), but had been estimated by Mittelman (1978) to be 170 x 10^{-6} mg/kg body weight/day (about twice the current estimate). Mittelman (1978) estimated the dietary exposure to NDPA to be 1920 x 10^{-12} mg/kg body weight/day (about two orders of magnitude higher than the current estimate). The Agency had not previously estimated dietary exposure to C_7/C_8 nitrosamine impurities. Because the current exposure estimates for NDPA are lower than those presented in the PD 1/2/3, the potential risk associated with exposure to NDPA will also be expected to be lower.

The dietary exposure figures in Table 2 are used to calculate the potential risk discussed in Section II. C. of this document.

2. Mixer/Applicator/Loader Exposure.

a. Factors Applied to Exposure Data.

The PD 1/2/3 presented estimates for both inhalational and dermal exposure to NDPA for mixer/applicator/loaders handling Treflan® EC. Because the NDPA levels have been reduced, as explained in the previous section, the inhalational and dermal estimates presented in the PD 1/2/3 (from Mittelman, 1978) have been divided by 50, reflecting a decrease in NDPA contamination in Treflan® EC from 5 ppm to an average of 0.10 ppm.

In calculating the inhalational exposure estimates for the PD 1/2/3, the Agency assumed a breathing rate in the workers of 1.2 cubic meters per hour. The Agency now has determined that a breathing rate of 1.8 cubic meters per hour more closely approximates the air intake for the type of work done by mixer/applicator/loaders and field workers. This figure is used in the determination of exposure estimates for all three chemicals, trifluralin, NDPA, and C_7/C_8 nitrosamines, for workers performing reentry activities as well. Inhalational estimates for trifluralin are derived from Mittelman (1978) and assume, as stated above, a breathing rate of 1.8 cubic meters per hour.

In order to estimate dermal exposure for trifluralin, it is necessary to determine what the percentage of dermal penetration would be. However, no data exist on the dermal absorption of trifluralin; thus an estimate, based on its physical chemical properties, was obtained. Trifluralin is a solid material, having a melting point of 48.5 to 49.0°C, and is essentially insoluble in water, but is soluble in acetone, ethanol, and xylene. In order to penetrate the dermis to any appreciable amount, a solid must be soluble in both water and organic solvents. Trifluralin would be expected to have, therefore, a maximum absorption of no more than one percent as an upper limit. When the emulsifiable concentrate (Treflan® EC) is added to water for application, a microcrystalline suspension of the solid is formed and dermal absorption would also not be expected to be above 1 percent (Zendzian, 1981a).

The dermal exposure estimates for trifluralin were derived from Mittelman (1978) and take into account the 1 percent dermal penetration figure. The dermal estimates apply to applicators only. It is assumed (Mittelman, 1978) that mixer/loaders wear suitable protective clothing as required on the Treflan® labels, so that no dermal exposure to these particular workers would normally be expected.

In calculating the dermal exposure estimates for NDPA in the PD 1/2/3 the Agency assumed a dermal penetration of 22 percent as suggested by the CAG (1978) based on a dermal absorption study in rats submitted by Elanco (1978b). If a worker was exposed to NDPA as a vapor or particulate matter, it was assumed only 22 percent of that would actually penetrate the skin. This figure is used in this document as well, to arrive at dermal exposure estimates for NDPA.

To obtain inhalational and dermal estimates for the C_7/C_8 nitrosamines (not previously calculated), the NDPA values (Mittelman), 1978) were divided by 50 (as described above for NDPA) and then by 5, since the C_7/C_8 nitrosamines (0.02 ppm) are assumed on the average to be present in Treflan® EC at one-fifth the average concentration of NDPA (0.10 ppm) (Elanco, 1980b). In the absence of actual monitoring data for the C_7/C_8 nitrosamines this approach is considered reasonable and is assumed to result in the best available estimate (Regelman, 1981b). Since no dermal penetration data are available for the C_7/C_8 nitrosamines the dermal penetration is assumed to be 100 percent reflecting an upper limit for dermal exposure (Zendzian, 1981b).

Table 3 presents the current inhalational and dermal estimates for mixer/applicator/loaders for all three chemicals. The footnotes in Table 3 indicate where all the various factors discussed in this section have been applied to the data. Mittelman's data (1978) have been included in this document as Appendix C, which is available on request.

b. Summary of Mixer/Applicator/Loader Exposure Estimates.

The total (inhalational plus dermal) estimates of exposure to trifuralin for mixer/applicator/loaders range from 103 micrograms per year for "greens" to 2950.6 micrograms per year for sugarcane. The range for NDPA is from 1.1 X 10^{-3} micrograms per year for okra, greens, peppers, and cucumbers to 32.2 X 10^{-3} micrograms per year for sugarcane. For C_7/C_8 nitrosamines, the range is 0.72 x 10^{-3} for okra, greens, peppers, cucumbers to 20.98 x 10^{-3} for sugar cane. Commerical applicators for all crops would be exposed yearly to a total of 1082.7 micrograms trifluralin, 11.8 x 10^{-3} micrograms NDPA and 2.36 x 10^{-3} micrograms C_7/C_8 nitrosamines. Assumptions regarding rate and frequency of application are as described by Mittelman, (1978).

In the Treflan® PD 1/2/3, total (inhalational plus dermal) NDPA exposure to mixer/applicator loaders ranged from 0.18 micrograms per year for cucumbers and "greens" to 5.05 micrograms per year for sugarcane. Commercial applicators were exposed to 1.88 micrograms NDPA per year. These values are approximately two orders of magnitude higher than the more current estimates for NDPA as seen in Table 3. The difference primarily exists because new methods employed in the manufacturing of Treflan® have reduced the NDPA contamination by a factor of 50 from the levels present at the time the PD 1/2/3 was issued.

The exposure figures as presented in Table 3 were used to calculate the potential risks discussed in Section II. C. of this document. Because the exposure to NDPA is lower, the risk would also be expected to be lower than that presented in the PD 1/2/3.

3. Reentry Exposure

a. Exposure to Vapor or Particulate Matter in the Air

NDPA and C_7/C_8 Nitrosamines

The PD 1/2/3 stated that workers reentering fields previously treated with trifluralin could possibly be exposed to NDPA as a vapor. The PD 1/2/3 (page 77) concluded that the amount of exposure to NDPA as a vapor was negligible, partially due to rapid photodegradation, and that the risk was also negligible. The Agency has found no reason to alter that finding, especially considering that the NDPA contamination in Treflan® EC currently is lower by a factor of 50. Since this exposure to NDPA vapor is considered to be negligible, it is reasonable to conclude that the exposure to C_7/C_8 nitrosamines as a vapor would also be negligible (Regelman, 1981b). Similarly, Mittelman (1978) concluded that reentry exposure (inhalational and dermal) to NDPA from particulate matter in the air would be highly unlikely and if it did occur, the amount would be insignificant. It is reasonable to assume, therefore, that exposure to C_7/C_8 nitrosamines from particulates would likewise be insignificant (Regelman, 1981b).

Trifluralin

In order to determine inhalational and dermal exposure to trifluralin in the air as a vapor, the Agency used data from Mittelman (1978), and White et al. (1977). Mittelman (1978) estimated the worker reentry exposure to trifluralin resulting from a single application of 1 lb a.i./acre for several crops. In that estimate (Mittelman, 1978, Table 14), the air trifluralin levels were interpolated from a study by White et al. (1977). For this document, a regression analysis of the White, et al. data was performed, and estimates were interpolated from the best-fit line (Regelman 1981b). These data are presented in Table 4.

The number of days after treatment when each operation occurred were taken directly from Mittelman's Tables 8-13 (1978) and are summarized by crop in Table 5.

Table 3

TREFLAN EXPOSURE ESTIMATES - APPLICATOR/MIXER/LOADERS (ug/year)[a]

Crop	Trifluralin			NDPA[e]			C_7/C_8 Nitrosamines[g]		
	Inhal.[b,c]	Dermal[d]	Total	Inhalation	Dermal[f]	Total	Inhalation[h]	Dermal	Total
Soybeans	804	56.2	860.2	3.5×10^{-3}	5.8×10^{-3}	9.3×10^{-3}	0.70×10^{-3}	5.27×10^{-3}	5.98×10^{-3}
Cotton	689	45.6	734.6	3.2×10^{-3}	4.7×10^{-3}	7.9×10^{-3}	0.64×10^{-3}	4.27×10^{-3}	4.91×10^{-3}
Tomatoes	245	17.6	262.6	1.2×10^{-3}	1.8×10^{-3}	3.0×10^{-3}	0.24×10^{-3}	1.64×10^{-3}	1.88×10^{-3}
Cole Crops	295	21.1	316.1	1.0×10^{-3}	2.2×10^{-3}	3.2×10^{-3}	0.20×10^{-3}	2.00×10^{-3}	2.20×10^{-3}
Beans	459	31.6	490.6	2.0×10^{-3}	3.3×10^{-3}	5.3×10^{-3}	0.40×10^{-3}	3.00×10^{-3}	3.40×10^{-3}
Trees/Vines	454	31.6	485.6	2.0×10^{-3}	3.3×10^{-3}	5.3×10^{-3}	0.40×10^{-3}	3.00×10^{-3}	3.40×10^{-3}
Hops	1622	115.8	1737.8	6.9×10^{-3}	12.1×10^{-3}	19.0×10^{-3}	1.38×10^{-3}	11.00×10^{-3}	12.38×10^{-3}
Potatoes	304	21.1	325.2	1.3×10^{-3}	2.2×10^{-3}	3.5×10^{-3}	0.26×10^{-3}	2.00×10^{-3}	2.26×10^{-3}
Carrots	491	35.1	526.1	2.1×10^{-3}	3.7×10^{-3}	5.8×10^{-3}	0.42×10^{-3}	3.36×10^{-3}	3.78×10^{-3}
Okra	100	7.0	107.0	0.4×10^{-3}	0.7×10^{-3}	1.1×10^{-3}	0.08×10^{-3}	0.64×10^{-3}	0.72×10^{-3}
Greens[i]	96	7.0	103.0	0.4×10^{-3}	0.7×10^{-3}	1.1×10^{-3}	0.08×10^{-3}	0.64×10^{-3}	0.72×10^{-3}
Spanish Peanuts	372	24.6	396.6	1.7×10^{-3}	2.6×10^{-3}	4.3×10^{-3}	0.34×10^{-3}	2.36×10^{-3}	2.70×10^{-3}
Celery	791	56.2	847.2	3.4×10^{-3}	5.8×10^{-3}	9.2×10^{-3}	0.68×10^{-3}	5.27×10^{-3}	5.95×10^{-3}
Peppers	100	7.0	107.0	0.4×10^{-3}	0.7×10^{-3}	1.1×10^{-3}	0.08×10^{-3}	0.64×10^{-3}	0.72×10^{-3}
Mint	1277	91.3	1368.3	5.4×10^{-3}	9.5×10^{-3}	14.9×10^{-3}	1.08×10^{-3}	8.64×10^{-3}	9.72×10^{-3}
Dill	541	38.6	579.6	2.3×10^{-3}	4.0×10^{-3}	6.3×10^{-3}	0.46×10^{-3}	3.64×10^{-3}	4.10×10^{-3}
Alfalfa	491	35.1	526.1	2.1×10^{-3}	3.7×10^{-3}	5.8×10^{-3}	0.42×10^{-3}	3.36×10^{-3}	4.78×10^{-3}
Spring Wheat	2413	172.0	2585.0	10.2×10^{-3}	17.9×10^{-3}	28.1×10^{-3}	2.04×10^{-3}	16.27×10^{-3}	18.31×10^{-3}
Mustard	813	56.2	869.2	3.6×10^{-3}	5.8×10^{-3}	9.4×10^{-3}	0.72×10^{-3}	5.27×10^{-3}	5.99×10^{-3}
Safflower	1922	136.9	2058.9	8.2×10^{-3}	14.2×10^{-3}	22.4×10^{-3}	1.64×10^{-3}	12.91×10^{-3}	14.55×10^{-3}
Sunflower	913	63.2	976.2	4.0×10^{-3}	6.6×10^{-3}	10.6×10^{-3}	0.80×10^{-3}	6.00×10^{-3}	6.80×10^{-3}
Sugar Beets	986	70.2	1056.2	4.2×10^{-3}	7.3×10^{-3}	11.5×10^{-3}	0.84×10^{-3}	6.64×10^{-3}	7.44×10^{-3}
Sugar Cane	2754	196.6	2950.6	11.7×10^{-3}	20.5×10^{-3}	32.2×10^{-3}	2.34×10^{-3}	18.64×10^{-3}	20.98×10^{-3}
Cucumbers	100	7.0	107.0	0.4×10^{-3}	0.7×10^{-3}	1.1×10^{-3}	0.08×10^{-3}	0.64×10^{-3}	0.72×10^{-3}
Cantaloupes	200	14.0	214.0	0.9×10^{-3}	1.5×10^{-3}	2.4×10^{-3}	0.18×10^{-3}	1.36×10^{-3}	1.54×10^{-3}
Watermelons	150	10.5	160.5	0.6×10^{-3}	1.1×10^{-3}	1.7×10^{-3}	0.12×10^{-3}	1.00×10^{-3}	1.12×10^{-3}
Dry Peas	858	59.7	917.7	3.8×10^{-3}	6.2×10^{-3}	10.0×10^{-3}	0.76×10^{-3}	5.64×10^{-3}	6.40×10^{-3}
English Peas	254	17.6	271.6	1.1×10^{-3}	1.8×10^{-3}	2.9×10^{-3}	0.22×10^{-3}	1.64×10^{-3}	1.86×10^{-3}
Field Peas	254	17.6	271.6	1.1×10^{-3}	1.8×10^{-3}	2.9×10^{-3}	0.22×10^{-3}	1.64×10^{-3}	1.86×10^{-3}
Commercial Applicators (all crops)	1009	73.7	1082.7	4.1×10^{-3}	7.7×10^{-3}	11.8×10^{-3}	0.82×10^{-3}	7.00×10^{-3}	7.82×10^{-3}

FOOTNOTES (Table 3)

a/ Derived from Mittelman (1978) Table 7. For cucumber, cantaloupe, watermelon, dry peas, English peas, field peas, greens, hops, celery, and dill, derived from addendum to Table 7.

b/ Assumes a breathing rate of 1.8 m^3/hr.

c/ Inhalation exposure values were estimated as follows:

$$\begin{array}{l}\text{Inhalation}\\ \text{Exposure}\\ \text{(soybeans)}\end{array} = \left[\begin{array}{c}\text{hrs/year}\\ \text{(application)}\end{array} \times \begin{array}{c}\text{breathing}\\ \text{rate (m}^3\text{/hr)}\end{array} \times \begin{array}{c}\text{ug/m}^3\text{ in air}\\ \text{(application)}\end{array}\right] + \left[\begin{array}{c}\text{hrs/year}\\ \text{(mixing/loading)}\end{array} \times \begin{array}{c}\text{breathing}\\ \text{rate (m}^3\text{/hr)}\end{array} \times \begin{array}{c}\text{ug/m}^3\text{ in air}\\ \text{(mixing/loading)}\end{array}\right]$$

$$= [16 \text{ hrs/year} \times 1.8 \text{ m}^3\text{/hr} \times 25.3 \text{ ug/m}^3] + [1.7 \text{ hrs/year} \times 1.8 \text{ m}^3\text{/hr} \times 24.6 \text{ ug/m}^3]$$

$$= 728.64 \text{ ug/year (application)} + 75.28 \text{ ug/year (mixing/loading)}$$

$$= \underline{804 \text{ ug/year}}$$

d/ Dermal exposure estimates (1/) were reduced by a factor of 0.01, to reflect the upper limit assumption of 1% dermal penetration. It was also assumed that workers during mixing/loading wear suitable protective clothing, so that no exposure during this phase of Treflan® usage was anticipated. Dermal exposure values were estimated as follows:

$$\begin{array}{l}\text{Trifluralin}\\ \text{Dermal Exposure}\\ \text{(soybeans)}\end{array} = \begin{array}{c}\text{hrs/year}\\ \text{application}\end{array} \times \begin{array}{c}\text{ug/hr dermal}\\ \text{exposure}\end{array} \times 0.01$$

$$= 16 \text{ hrs/year} \times 351 \text{ ug/hr} \times 0.01 = \underline{56.2 \text{ ug/year}}$$

e/ Total nitrosamine levels (Mittelman, 1978) were reduced by a factor of 50, reflecting the 50-fold reduction in average nitrosamine contamination since earlier estimates (PD 1/2/3) were made (0.1 ppm vs. 5.0 ppm = 1:50).

f/ Dermal exposure estimate figures (Mittelman, 1978) have been reduced by a factor of 0.22, reflecting an upper limit dermal penetration of 22% (PD 1/2/3).

g/ Derived by dividing the Mittelman (1978) NDPA exposure estimates by 50 (see 5/ above) and then by 5, since the average C_7/C_8 nitrosamine contamination is now approximately 20% of the average NDPA levels (Elanco, 1980f).

h/ Since no dermal penetration data are available for C_7/C_8 nitrosamines, 100% dermal absorption is assumed as an upper limit (Zendzian, 1981b).

i/ Greens includes mustard greens, turnip greens, collards and kale.

Table 4

Estimated Trifluralin Concentrations in Air as a Vapor After Treatment[a]

Days After Treatment	0	3	7	14	18	30	35
ug/m^3	0.26	0.23	0.20	0.15	0.13	0.08	0.07
Days After Treatment	40	42	45	56	63	79	98
ug/m^3	0.06	0.05	0.05	0.03	0.02	0.01	0.01

---

[a] Data were taken from Mittelman's Table 14 (1978). A regression analysis was used to approximate the best line, from which the data were then interpolated.

Table 5

Number of Days After Trifluralin Treatment When Each Operation Occurred

	2nd Incorporation	Planting	Irrigation	Tillage	Seeding	Hand Hoeing	Insect Scouting	Harvest
Soybeans	14	14+	-	40	-	-	-	210
Cotton	30	30	30/90	63	-	79	112	225
Beans	7	18	56	42	-	-	-	98
Tomatoes	-	-	45	42	3	35	-	105
Tree/Vine	3	7	118	134	-	-	-	210
Cole Crops	3	-	45	45	3	42	-	105

The estimated air concentrations of trifluralin at each specified post-application interval are summarized in Table 6, using the data from Tables 4 and 5. For example, during the second incorporation, 14 days after treatment (from Table 5) exposure of workers to trifluralin would be 0.15 ug/m^3 (from Table 4). Since the measurements of levels of trifluralin in air became increasingly unreliable at or near the limit of detection, values below 0.01 ug/m^3 were assumed to be zero, and were deleted from Table 6. Estimated hours of exposure per operation per year were taken directly from Mittelman (1978), and summarized in Table 7.

Finally, reentry exposure to trifluralin as a vapor in the air was computed, and summarized by operation, in Table 8 using values from Table 6 and 7. Mittelman (1978) calculated that dermal exposure would be about 12 times inhalational exposure based on the data from White et al. (1977). This factor was applied to the estimated inhalation values, and summarized in the "dermal" column. The final column reflects total estimated annual reentry exposure in micrograms per year by crop.

Theoretically, workers reentering trifluralin treated fields could inhale or be dermally exposed to trifluralin adsorbed to soil particulate matter in the air. Mittelman (1978) in citing soil concentration data from the White et al. study (1977) calculated that the upper limit exposure would be approximately 1.28 micrograms per year for tree and vine culture. The calculation made was an extrapolation from the White et al. study. The exposure was stated by Mittelman (1978) to be insignificant. Thus, the Agency concludes that any possible inhalational or dermal exposure to trifluralin from airborne soil particles during reentry would be negligible.

b. Dermal Exposure From Contact with the Soil

Although dermal exposure to trifluralin, NDPA and the C_7/C_8 nitrosamines from contact with soil during reentry into treated fields may occur, it is difficult to quantify due to the variety of: the field activities performed, the degree of physical contact with the soil by workers, the amount of exposed body area, the duration of exposure, and the degree of dermal penetration of the particular chemical involved.

The PD 1/2/3 stated that reentry dermal exposure to NDPA in the soil was theoretically possible and presented a method for arriving at an estimate. An assumption was made at the time that "a uniform layer of soil forms a film on the uncovered skin 1.0 millimeter thick." This resulted in an accumulation of soil on the skin amounting to 870 grams or approximately 2 pounds. Elanco [30000/32:#6], as discussed later in Section III of this document, claimed this was an unreasonable assumption. Although that approach was used only to describe an upper limit of possible exposure, the Agency agrees with Elanco that the figure is excessive and is currently using a different approach to calculate dermal exposure.

Table 6[a]

Estimated Air Concentration of Trifluralin (ug/m^3)

	2nd Incorporation	Planting	Irrigation	Tillage	Seeding	Hand Hoeing	Harvest
Soybeans	.15	.15	-	.06	-	-	-
Cotton	.08	.08	.03	.02	-	.01	-
Beans	.20	.13	.05	.03	-	-	.01
Tomatoes	-	-	.05	.05	.23	.07	-
Tree/Vine	.23	.20	-	-	-	-	-
Cole Crops	.23	-	.05	.05	.23	.05	-

---

[a] Values were taken from Table 4. Entries have been deleted if the trifluralin concentration was below 0.01 ug/m^3.

Table 7

Estimated Hours of Exposure per Year

	2nd Incorporation	Planting	Irrigation	Tillage	Seeding	Hand Hoeing	Harvest
Soybeans	8	10	-	20	-	-	-
Cotton	13	11	2	33	-	13	-
Beans	6	13	8	20	-	-	32
Tomatoes	-	-	8	5	8	125	-
Tree/Vine	6	24	-	-	-	-	-
Cole Crops	3	-	12	6	6	16	-

Table 8

Estimated Reentry Exposure to Trifluralin Vapor in the air (ug/year)[a]

	2nd Incorporation	Planting	Irrigation	Tillage	Seeding	Hand Hoeing	Harvest	Inhalation	Dermal[b]	Total
Soybeans	2.16	2.7	-	2.16	-	-	-	7.02	84.24	91.3
Cotton	1.87	1.58	0.29	1.19	-	0.23	-	5.16	61.92	67.1
Beans	2.16	3.04	0.72	1.08	-	-	0.58	7.58	90.96	98.5
Tomatoes	-	-	0.72	0.48	3.31	15.75	-	20.23	242.76	263.0
Tree/Vine	2.48	8.64	-	-	-	-	-	11.12	133.44	144.6
Cole Crops	1.24	-	1.08	0.54	2.48	1.44	-	6.78	81.36	88.1

[a] ug/m^3 x hrs/year x 1.8 m^3/hr = ug trifluralin/year.

[b] Mittelman (1978) assumed dermal exposure to be 12 times inhalation exposure.

Dermal exposure to trifluralin would be expected to be low (Regelman, 1981b). Exposure to the nitrosamines should be much lower, since levels in Treflan® EC have been reduced about 50-fold in recent years. Exposure estimates for trifluralin and nitrosamines have however been calculated by the Agency (Regelman, 1981b and 1981c). In one study which appears to be typical of Treflan® usage, West and Day (1977) analyzed soils from fields treated at application rates of 0.5-1.0 lb. a.i./acre. Trifluralin residues in the surface-to-3-inch layer of top-soil ranged from 0.09-0.63 ppm (0.09 - 0.63 ug/gm soil), 26 to 176 days after treatment. NDPA was quantified at levels up to 0.19 ug/kg soil 26 days after application of 0.75 lb a.i./acre. The trifluralin used contained from 78-252 ppm NDPA. The NDPA figure may be adjusted downward by a factor of about 1650[1/] reflecting NDPA levels in currently produced Treflan® E.C. with an average of 0.1 ppm. Thus NDPA levels could be estimated at 1.2×10^{-7} ug/gm soil.

Jensen (1981) stated that approximately 1 gram of talcum powder would cover 0.082 m^2 of skin (equivalent to 12.2 gm/m^2). Assuming that talcum powder and dirt have about the same densities[2/], and assuming that a worker entering a treated field has a total uncovered skin surface area of about 0.29 m^2 (Mittelman, 1978), the total amount of soil on the skin could be about 4 grams, a figure much lower than the 870 grams estimated in the PD 1/2/3.

Soil could contain about 2.5 ug trifluralin (0.63 ug/gm x 4 gm), about 5×10^{-7} ug NDPA (1.2×10^{-7} ug/gm x 4 gm), and about 1×10^{-7} ug C_7/C_8 nitrosamines, assuming a ratio of 5:1 between NDPA and C_7/C_8 nitrosamines.

For purposes of this exposure analysis, if we assume an average of ten separate exposures per year, the total annual dermal reentry exposure could be as high as 25 ug trifluralin, 5×10^{-6} ug NDPA and 1×10^{-6} ug C_7/C_8 nitrosamines (Regelman, 1981b).

It is reasonable to conclude that these dermal reentry exposure estimates are upper-limit values, since photodegradation, soil metabolism and other degradative and metabolic pathways, as well as probable dermal penetration below 100 percent would be expected to reduce exposure to levels below these estimates (Regelman, 1981b).

The Agency does not believe, therefore, that the exposure estimates for NDPA (no greater than 5×10^{-6} micrograms per year) and C_7/C_8 nitrosamines (1×10^{-6} micrograms per year) are reliable at these extremely low levels. Actual exposure may be orders of magnitude lower. The Agency must conclude, then, that reentry dermal exposure to these nitrosamines from soil is likely to be negligible (Regelman, 1981c).

[1/] $\frac{78+252}{2}$: 1 = 1650:1

[2/] Handbook of Chemistry and Physics, Robert C. Weast, Ed. Chemical Rubber Publishing Company, 54th Edition, 1973-1974.

Table 9 summarizes the reentry exposure to trifluralin in the air as a vapor and in the soil adsorbed to soil particles (Regelman, 1981b). No reentry exposure estimates are given for the nitrosamines because, as explained above, inhalational or dermal exposure to nitrosamines in the air (as a vapor or adsorbed to particulate matter) or in the soil, is likely to be negligible. The trifluralin inhalational and dermal exposure estimates (Table 9) were used to calculate the potential risk estimates to reentry worker presented in Section II. C. of this document.

C. Revised Cancer Risk Estimate.

1. Rationale for Revisions

a. NDPA

The dietary and worker cancer risk estimates found in the PD 1/2/3 presented estimates for NDPA only. The Agency assumed at that time that the cancer risk from trifluralin itself was zero, since there were no data which indicated otherwise. When the Agency received data (Elanco, 1980d) which showed that trifluralin itself appeared to be associated with production of tumors and analyses which revealed contamination from C_7/C_8 nitrosamines in addition to NDPA (Elanco, 1978a, 1980b, and 1981), it became necessary to recalculate the risk, taking these two additional chemicals (trifluralin and C_7/C_8 nitrosamines) into account.

In the PD 1/2/3, the Agency used the "one-hit" model to calculate the slope parameter or potency of NDPA as a carcinogen, using only the lowest dose showing a significant response from data by Druckrey et al., 1967. Recently, the Agency has decided the "multistage" model provides a betterestimate for the slope parameter; it incorporates data from all the dosed groups, both high and low, and is a generalization of the "one-hit" model. It encompasses the "one-hit" model as a special case (Chen and Haberman, 1981).

The NDPA slope parameter estimated in the PD 1/2/3 was 0.4 per ppm. It was assumed that the ppm dietary consumption was equivalent between humans and animals. The Agency has reevaluated this assumption and has concluded that it is not justified, since the calories per kilogram of food are very different in the diet of man as compared to laboratory animals, primarily due to the moisture content difference (Chen and Haberman, 1981). It is more accurate to calculate the slope per milligram per kilogram body weight per day.

Therefore, the Agency (Chen and Haberman, 1981) recalculated the slope for NDPA based on liver tumor incidence in male rats as reported by Druckery et al, (1967) as shown in Table 10. Using the "multistage" model, the human carcinogenic potency for NDPA is estimated as follows:

$$q^*_1 = 0.62 \times (70/0.35)^{1/3}$$

$$= 3.6 \text{ (mg/kg body weight/day)}^{-1}$$

Table 9

Reentry Exposure to Trifluralin (ug/year)

	Trifluralin Vapor a/c/		Trifluralin in the Soil a/	
	Inhalation	Dermal b/	Dermal b/d/	Total
Soybeans	7.0	0.84	0.25	8.09
Cotton	5.2	0.62	0.25	6.07
Beans	7.6	0.91	0.25	8.76
Tomatoes	20.2	2.43	0.25	22.88
Tree/Vine	11.1	1.33	0.25	12.68
Cole Crops	6.8	0.81	0.25	7.86

a/ Regelman (1981b and 1981c).

b/ The dermal exposure figures were reduced by a factor of 0.01, reflecting a 1% upper limit for dermal absorption (Zendzian, 1981a).

c/ Mittleman, 1978, stated that exposure to trifluralin particulate matter in the air would be insignificant.

d/ Assumes 10 separate exposures per year, (Regelman, 1981b).

Table 10

Liver Tumor Incidence in Male Rats Given NDPA[a]

Dose (mg/kg/day)	0[b]	4	8	15
Response	1/30	12/14	15/16	15/15

---

[a] Druckery et al, 1967.

[b] A control incidence of 1/30 is used in the calculation. The frequency of spontaneous malignant tumors was about 1 percent up to the age of 500 days.

b. Trifluralin

An estimate of carcinogenic potency of trifluralin is based on data in Table 11 taken from the chronic feeding study done by Elanco (1980d).

Using the "multistage" model, the human carcinogenic potency for trifluralin is estimated as follows (Chen and Haberman, 1981):

$$q^*_1 = 1.31 \times 10^{-3} \times (70/0.35)^{1/3}$$

$$= 7.7 \times 10^{-3} \text{ (mg/kg body weight/day)}^{-1}$$

When this number is compared with the slope or potency for NDPA of 3.6, it is evident that NDPA is the more potent carcinogen by approximately 3 orders of magnitude.

c. C_7/C_8 Nitrosamines

No data exist on C_7/C_8 nitrosamine contaminants in Treflan® regarding the potential for producing carcinogenic effects. The Agency's nitrosamine policy states:

> "In the absence of acceptable oncogenic testing with the specific N-nitroso compound, the Agency will assume that the contaminant is as potent as a carcinogen as N-nitrosodiethylamine." [45 FR 42854].

Therefore, the Agency used data on liver tumors produced in male rats which had been administered N-nitrosodiethylamine, also called diethyl N-nitrosamine (DENA), as reported by Druckrey et al., (1967) and shown in Table 12.

Using the "multistage" model and data for DENA (Druckery et al., 1967), the carcinogenic potency for C_7/C_8 nitrosamines is estimated as follows (Chen and Haberman, 1981):

$$q^*_1 = 5.72 \times (70/0.35)^{1/3}$$

$$= 33 \text{ (mg/kg body weight/day)}^{-1}$$

When compared with the potencies of trifluralin and NDPA (7.7×10^{-3} and 3.6, respectively), it can be seen that the C_7/C_8 nitrosamines, assumed to be as carcinogenic as DENA, are potentially more carcinogenic. As will be seen, however, the extent of actual exposure to the three chemicals in Treflan® influences the degree of risk associated with each one.

2. Dietary Risk

The Agency calculated the risk of cancer from potential dietary exposure to trifluralin, NDPA, and C_7/C_8 nitrosamines by using the slopes as given above and the dietary exposure estimates given in Table 2, discussed in Section II. B. of this document. The exposures and risks are presented in Table 13.

Table 11

Combined Kidney, Urinary Bladder, and Thyroid Tumors in Male Rats Given Trifluralin[a/]

Dose (mg/kg/day)	0	30	128	272
Response[b/]	5/60	5/60	9/60	17/60

[a/] Elanco, 1980d.

[b/] In order to be counted as a "response", each rat had to have at least one tumor of the kidney, urinary bladder, or thyroid.

Table 12

Liver Tumor Incidence in Male Rats Given DENA in Drinking Water[a]

Dose (mg/kg/day)	0	0.075	0.15	0.30
Response[b]	1/30[b]	1/7[c]	27/30	67/67

[a] Druckery, et al, 1967.

[b] As in Table 10, the control incidence of 1/30 is used.

[c] If all tumor types were considered, the incidence would be 5/7.

Table 13

Dietary Risk[a] - Trifluralin, NDPA and C_7/C_8 Nitrosamines

Commodity	Trifluralin[b] Daily Intake mg/kg diet	Trifluralin[b] Lifetime Risk[e]	NDPA[c] Daily Intake mg/kg diet	NDPA[c] Lifetime Risk	C_7/C_8 Nitrosamines[d] Daily Intake mg/kg diet	C_7/C_8 Nitrosamines[d] Lifetime Risk
Asparagus	14.00×10^{-6}	0.025×10^{-7}	3.15×10^{-12}	0.03×10^{-11}	0.63×10^{-12}	0.05×10^{-11}
Barley	0.21×10^{-6}	0.000×10^{-7}	0.05×10^{-12}	0.00×10^{-11}	0.01×10^{-12}	0.00×10^{-11}
Carrots	1257.36×10^{-6}	2.234×10^{-7}	282.55×10^{-12}	2.35×10^{-11}	56.51×10^{-12}	4.30×10^{-11}
Citrus Fruit	30.10×10^{-6}	0.054×10^{-7}	6.76×10^{-12}	0.06×10^{-11}	1.35×10^{-12}	0.10×10^{-11}
Corn, grain	100.00×10^{-6}	0.178×10^{-7}	22.47×10^{-12}	0.19×10^{-11}	4.49×10^{-12}	0.34×10^{-11}
Cottonseed	10.43×10^{-6}	0.018×10^{-7}	2.34×10^{-12}	0.02×10^{-11}	0.47×10^{-12}	0.04×10^{-11}
Cucurbits,						
Cantaloupe	5.20×10^{-6}	0.009×10^{-7}	1.17×10^{-12}	0.01×10^{-11}	0.23×10^{-12}	0.02×10^{-11}
Cucumber	21.24×10^{-6}	0.038×10^{-7}	4.77×10^{-12}	0.04×10^{-11}	0.95×10^{-12}	0.07×10^{-11}
Watermelon	42.90×10^{-6}	0.076×10^{-7}	9.64×10^{-12}	0.08×10^{-11}	1.93×10^{-12}	0.15×10^{-11}
Dill	1.61×10^{-6}	0.003×10^{-7}	0.36×10^{-12}	0.00×10^{-11}	0.07×10^{-12}	0.00×10^{-11}
Fruiting Vegetables,						
Green Peppers	4.54×10^{-6}	0.008×10^{-7}	1.02×10^{-12}	0.01×10^{-11}	0.20×10^{-12}	0.02×10^{-11}
Tomatoes	197.46×10^{-6}	0.351×10^{-7}	44.37×10^{-12}	0.37×10^{-11}	8.87×10^{-12}	0.68×10^{-11}
Grapes/Raisins	3.87×10^{-6}	0.007×10^{-7}	0.87×10^{-12}	0.01×10^{-11}	0.17×10^{-12}	0.01×10^{-11}
Hops	0.75×10^{-6}	0.001×10^{-7}	0.17×10^{-12}	0.00×10^{-11}	0.03×10^{-12}	0.00×10^{-11}
Leafy Vegetables,						
Broccoli	6.50×10^{-6}	0.012×10^{-7}	1.46×10^{-12}	0.01×10^{-11}	0.29×10^{-12}	0.02×10^{-11}
Brussel Sprouts	1.95×10^{-6}	0.003×10^{-7}	0.44×10^{-12}	0.00×10^{-11}	0.09×10^{-12}	0.01×10^{-11}
Cabbage	49.21×10^{-6}	0.087×10^{-7}	11.06×10^{-12}	0.09×10^{-11}	2.21×10^{-12}	0.17×10^{-11}
Cauliflower	3.82×10^{-6}	0.007×10^{-7}	0.86×10^{-12}	0.01×10^{-11}	0.17×10^{-12}	0.01×10^{-11}
Celery	11.43×10^{-6}	0.020×10^{-7}	2.57×10^{-12}	0.02×10^{-11}	0.51×10^{-12}	0.04×10^{-11}
Collard	7.68×10^{-6}	0.014×10^{-7}	1.73×10^{-12}	0.01×10^{-11}	0.35×10^{-12}	0.03×10^{-11}
Kale	2.88×10^{-6}	0.005×10^{-7}	0.65×10^{-12}	0.00×10^{-11}	0.13×10^{-12}	0.01×10^{-11}
Mustard Greens	5.15×10^{-6}	0.009×10^{-7}	1.16×10^{-12}	0.01×10^{-11}	0.23×10^{-12}	0.02×10^{-11}
Turnip Greens	2.89×10^{-6}	0.005×10^{-7}	0.65×10^{-12}	0.00×10^{-11}	0.13×10^{-12}	0.01×10^{-11}
Others	133.00×10^{-6}	0.236×10^{-7}	29.89×10^{-12}	0.25×10^{-11}	5.98×10^{-12}	0.45×10^{-11}

Table 13 (continued)

Dietary[a/] Risk - Trifluralin, NDPA and C_7/C_8 Nitrosamines

Commodity	Trifluralin[b/] Daily Intake mg/kg diet	Trifluralin[b/] Lifetime Risk[e/]	NDPA[c/] Daily Intake mg/kg diet	NDPA[c/] Lifetime Risk	C_7/C_8 Nitrosamines[d/] Daily Intake mg/kg diet	C_7/C_8 Nitrosamines[d/] Lifetime Risk
Mung Beans (sprouts)	3.00×10^{-6}	0.005×10^{-7}	0.67×10^{-12}	0.00×10^{-11}	0.13×10^{-12}	0.01×10^{-11}
Mustard Seed	3.00×10^{-6}	0.005×10^{-7}	0.67×10^{-12}	0.00×10^{-11}	0.13×10^{-12}	0.01×10^{-11}
Nuts	0.79×10^{-6}	0.001×10^{-7}	0.18×10^{-12}	0.00×10^{-11}	0.04×10^{-12}	0.00×10^{-11}
Okra	7.00×10^{-6}	0.012×10^{-7}	1.57×10^{-12}	0.01×10^{-11}	0.31×10^{-12}	0.02×10^{-11}
Peanuts	7.06×10^{-6}	0.012×10^{-7}	1.59×10^{-12}	0.01×10^{-11}	0.32×10^{-12}	0.03×10^{-11}
Peppermint Oil	46.20×10^{-6}	0.082×10^{-7}	10.38×10^{-12}	0.09×10^{-11}	2.08×10^{-12}	0.16×10^{-11}
Root Crop Vegetables,						
Potatoes	28.78×10^{-6}	0.051×10^{-7}	6.47×10^{-12}	0.05×10^{-11}	1.29×10^{-12}	0.10×10^{-11}
Others	554.00×10^{-6}	0.984×10^{-7}	124.49×10^{-12}	1.03×10^{-11}	24.90×10^{-12}	1.95×10^{-11}
Safflower Seeds	3.00×10^{-6}	0.005×10^{-7}	0.67×10^{-12}	0.00×10^{-11}	0.13×10^{-12}	0.01×10^{-11}
Seed/Pod Vegtables,						
Beans	154.22×10^{-6}	0.274×10^{-7}	34.66×10^{-12}	0.29×10^{-11}	6.93×10^{-12}	0.53×10^{-11}
Soybeans	34.68×10^{-6}	0.062×10^{-7}	7.79×10^{-12}	0.06×10^{-11}	1.56×10^{-12}	0.12×10^{-11}
Peas	9.52×10^{-6}	0.017×10^{-7}	2.14×10^{-12}	0.02×10^{-11}	0.43×10^{-12}	0.03×10^{-11}
Sorghum, grain	0.06×10^{-6}	0.000×10^{-7}	0.01×10^{-12}	0.00×10^{-11}	0.00×10^{-12}	0.00×10^{-11}
Spearmint Oil	46.20×10^{-6}	0.082×10^{-7}	10.38×10^{-12}	0.09×10^{-11}	2.08×10^{-12}	0.16×10^{-11}
Stone Fruits	125.00×10^{-6}	0.222×10^{-7}	28.09×10^{-12}	0.23×10^{-11}	5.62×10^{-12}	0.43×10^{-11}
Sugar, Cane & Beet	42.59×10^{-6}	0.076×10^{-7}	9.57×10^{-12}	0.08×10^{-11}	1.91×10^{-12}	0.15×10^{-11}
Sunflower Seeds	1.95×10^{-6}	0.003×10^{-7}	0.44×10^{-12}	0.00×10^{-11}	0.09×10^{-12}	0.01×10^{-11}
Wheat Grain and Straw	11.40×10^{-6}	0.020×10^{-7}	2.56×10^{-12}	0.02×10^{-11}	0.51×10^{-12}	0.04×10^{-11}
TOTALS	2.98×10^{-3}	5.30×10^{-7}	6.72×10^{-10}	5.85×10^{-11}	1.34×10^{-10}	1.03×10^{-10}

a/ Data from E. Regelman (1981a)

b/ Trifluralin risk slope = 7.7×10^{-3}/mg/kg body weight/day.

c/ NDPA risk slope = 3.6/mg/kg body weight/day.

d/ C_7/C_8 risk slope was assumed to be as large as the diethylnitrosamine risk slope of 33/mg/kg body weight/day.

e/ Lifetime risk = Intake (mg/kg diet/day) $\times \frac{\text{1.5 kg diet/day}}{\text{65 kg Body Weight}} \times$ risk slope (/mg/kg body weight/day).

a. Trifluralin

In order to calculate the risk to the general population from dietary exposure to trifluralin, the Agency used the following formula:

Lifetime Individual Risk = slope x exposure

where the slope for trifluralin is 7.7×10^{-3} (mg/kg body weight/day)$^{-1}$ and where the exposure is a product of

$$\text{daily intake (mg/kg diet/day)} \times \frac{1.5 \text{ kg diet/day}}{65 \text{ kg body weight.}}$$

This assumes an average daily intake of 1.5 kilograms of food a day for the average 65 kilogram person. Thus, for example, the lifetime individual risk (R) from exposure to trifluralin from eating carrots (Table 13) is:

$$R = 7.7 \times 10^{-3} \times [(1257.36 \times 10^{-6}) \times \frac{1.5}{65}]$$

$$= 2.234 \times 10^{-7}$$

The risk associated with eating carrots is the highest; the risk associated with all other crops is less than 1×10^{-7}. The total lifetime individual risk from exposure to trifluralin in Treflan® in the daily diet is 5.30×10^{-7}.

b. NDPA

Similarly, the lifetime individual risk (R) from NDPA on carrots (Table 13) in the diet is:

$$R = 3.6 \times [(292.55 \times 10^{-12}) \times \frac{1.5}{65}]$$

$$= 2.35 \times 10^{-11}$$

The risks assoiated with other crops are less than 1.5×10^{-11}. The total lifetime individual risk from exposure to the NDPA in Treflan® in the daily diet is 5.85×10^{-11}.

c. C_7/C_8 Nitrosamines

The lifetime individual risk (R) from C_7/C_8 nitrosamines on carrots (Table 13) in the diet, assuming the slope to be as large as for DENA, is:

$$R = 33 \times [(56.51 \times 10^{-12}) \times \frac{1.5}{65}]$$
$$= 4.30 \times 10^{-11}$$

The risks associated with exposure to all other crops are less than 2×10^{-11}. The total lifetime individual risk from exposure to the C_7/C_8 nitrosamines in Treflan® in the daily diet is 1.03×10^{-10}.

d. Comparison of Dietary Risk Estimates with Those of the PD 1/2/3

The risk associated with exposure to NDPA as calculated in the PD 1/2/3 is higher than that calculated in this document. The Agency calculated in the PD 1/2/3 that the highest lifetime individual dietary risk associated with nitrosamines (NDPA) was 8.7×10^{-9} for carrots. The analogous NDPA risk figure in Table 13 for carrots is 2.35×10^{-11} and for C_7/C_8 nitrosamines is 4.3×10^{-11}. The same relationship exists for the dietary risk from all crops listed in Table 13.

The total risk for NDPA in the PD 1/2/3 was 3.3×10^{-8}, computed by adding the risks associated with each crop. The figure in this document is 5.8×10^{-11} for NDPA and 1.03×10^{-10} for $C_7/_8$ nitrosamines, a risk lower by three and two orders of magnitude, respectively.

Three factors account for this difference. First, the Agency based exposure to NDPA on trifluralin residue data submitted by Elanco and summarized by Regelman (1981a), whereas in the PD 1/2/3 the Agency based exposure to NDPA on trifluralin tolerances, which are higher than the actual residues found by about a factor of 5.

The total dietary risk from exposure to Treflan® is currently 5.3×10^{-7}, obtained by adding risk from exposure to trifluralin (5.3×10^{-7}) with those associated with NDPA (5.85×10^{-11}) and C_7/C_8 nitrosamines (1.03×10^{-10}). The contribution to risk by NDPA and C_7/C_8 nitrosamines in insignificant. The risk is principally associated with trifluralin.

Second, current NDPA contamination in Treflan® is defined by a trifluralin to NDPA ratio of 445,000 ppm:0.1 ppm or 4,450,000:1. (Treflan® EC contains 44.5 percent trifluralin or 445,000 ppm.) The daily intake of NDPA was calculated by dividing the trifluralin daily intake by 4,450,000. The ratio used in the PD 1/2/3 was 89,000:1, reflecting a higher NDPA contamination (445,000 ppm trifluralin divided by 5 ppm NDPA). Therefore, because the NDPA exposure is calculated to be much less at the present time than previously, it follows that the risk would be less as well.

The third contributing factor to the difference between the risk associated with NDPA as calculated in the PD 1/2/3 and that calculated in this document is the use of the multistage mathematical model rather than the "one-hit" model to estimate the slope parameter used in the risk assessment.

The range for NDPA risk (Table 13) is from less than 0.01×10^{-11} for barley to 2.35×10^{-11} for carrots. The range for C7/C8 nitrosamines is from less than 0.01×10^{-11} for barley to 4.30×10^{-11} for carrots. Compared to a range in the PD 1/2/3 of 0.11×10^{-9} to 8.68×10^{-9} for sunflower and carrots, respectively, it can be seen that the cancer risk to the general population associated with exposure to the nitrosamines in Treflan® is currently significantly lower than was previously estimated.

The total lifetime individual cancer risk estimate in the PD 1/2/3 for the general population from exposure to Treflan® in the diet for all crops was 3.3×10^{-8} and was associated with the NDPA contaminant. In this document, the total dietary cancer risk estimate is 5.3×10^{-7}, principally from exposure to the trifluralin in Treflan® (Table 13).

Thus, the total risk associated with dietary exposure to Treflan® as calculated in the PD 1/2/3 has changed by approximately one order of magnitude; that is, the chance of getting cancer from dietary exposure to Treflan® has increased somewhat over that estimated when the PD 1/2/3 was issued, because of the association of trifluralin with the production of tumors in rats as discussed.

3. Mixer/Applicator/Loader Risk

a. Calculations and Assumptions

The Agency calculated the risk of cancer in workers from exposure to trifluralin, NDPA, and C_7/C_8 nitrosamines in Treflan® by using the slopes given in Section II.C. of this document and the mixer/applicator/loader exposure estimates given in Table 3. The total lifetime individual exposure (inhalational and dermal) and risks for each crop and each chemical are presented in Table 14.

To calculate the lifetime individual risk, the Agency used the following formula:

$$\text{Risk}^{(R)} = \text{slope} \times \text{exposure}$$

where the slopes (or potency) for trifluralin, NDPA, or C_7/C_8 nitrosamines were 7.7×10^{-3}, 3.6, and 33, respectively, in units of $(\text{mg/kg body weight/day})^{-1}$, as described in the Dietary Risk Section of this document. The lifetime individual exposure was calculated as follows:

$$\frac{\begin{array}{c}\text{Total Exposure}\\ \text{(micrograms per year)}\end{array}}{\text{365 days per year}} \times \frac{\begin{array}{c}\text{Working Lifetime}\\ \text{(40 years)}\end{array}}{\begin{array}{c}\text{average}\\ \text{lifetime}\end{array}} \times \frac{\text{1 Person}}{\begin{array}{c}\text{65 kg}\\ \text{(70 years)}\end{array}} \times \frac{\text{1 mg}}{\begin{array}{c}\text{1000}\\ \text{micrograms}\end{array}}$$

Table 14

TREFLAN RISK ESTIMATES - APPLICATOR/MIXER/LOADERS[a]

	Trifluralin[c]		NDPA[d]		C_7/C_8 Nitrosamines[e]	
Crop	Total Exposure (ug/year)	Lifetime Risk[b]	Total Exposure (ug/year)	Lifetime Risk	Total Exposure (ug/year)	Lifetime Risk
Soybeans	860.2	1.6×10^{-7}	9.3×10^{-3}	8×10^{-10}	5.98×10^{-3}	48×10^{-10}
Cotton	734.6	1.4×10^{-7}	7.9×10^{-3}	7×10^{-10}	4.91×10^{-3}	39×10^{-10}
Tomatoes	262.6	0.5×10^{-7}	3.0×10^{-3}	3×10^{-10}	1.88×10^{-3}	15×10^{-10}
Cole Crops	316.1	0.6×10^{-7}	3.2×10^{-3}	3×10^{-10}	2.20×10^{-3}	17×10^{-10}
Beans	490.6	0.9×10^{-7}	5.3×10^{-3}	5×10^{-10}	3.40×10^{-3}	27×10^{-10}
Trees/Vines	485.6	0.9×10^{-7}	5.3×10^{-3}	5×10^{-10}	3.40×10^{-3}	27×10^{-10}
Hops	1737.8	3.2×10^{-7}	19.0×10^{-3}	16×10^{-10}	12.38×10^{-3}	98×10^{-10}
Potatoes	325.2	0.6×10^{-7}	3.5×10^{-3}	3×10^{-10}	2.26×10^{-3}	18×10^{-10}
Carrots	526.1	1.0×10^{-7}	5.8×10^{-3}	5×10^{-10}	3.78×10^{-3}	30×10^{-10}
Okra	107.0	0.2×10^{-7}	1.1×10^{-3}	1×10^{-10}	0.72×10^{-3}	6×10^{-10}
Greens	103.0	0.2×10^{-7}	1.1×10^{-3}	1×10^{-10}	0.72×10^{-3}	6×10^{-10}
Spanish Peanuts	396.6	0.7×10^{-7}	4.3×10^{-3}	4×10^{-10}	2.70×10^{-3}	21×10^{-10}
Celery	847.2	1.6×10^{-7}	9.2×10^{-3}	8×10^{-10}	5.95×10^{-3}	47×10^{-10}
Peppers	107.0	0.2×10^{-7}	1.1×10^{-3}	1×10^{-10}	0.72×10^{-3}	6×10^{-10}
Mint	1368.3	2.5×10^{-7}	14.9×10^{-3}	13×10^{-10}	9.72×10^{-3}	77×10^{-10}
Dill	579.6	1.1×10^{-7}	6.3×10^{-3}	5×10^{-10}	4.10×10^{-3}	33×10^{-10}
Alfalfa	526.1	1.0×10^{-7}	5.8×10^{-3}	5×10^{-10}	4.78×10^{-3}	38×10^{-10}
Spring Wheat	2585.0	4.8×10^{-7}	28.1×10^{-3}	24×10^{-10}	18.31×10^{-3}	146×10^{-10}
Mustard	869.2	1.6×10^{-7}	9.4×10^{-3}	8×10^{-10}	5.99×10^{-3}	48×10^{-10}
Safflower	2058.9	3.8×10^{-7}	22.4×10^{-3}	19×10^{-10}	14.55×10^{-3}	116×10^{-10}
Sunflower	976.2	1.8×10^{-7}	10.6×10^{-3}	9×10^{-10}	6.80×10^{-3}	54×10^{-10}
Sugar Beets	1056.2	2.0×10^{-7}	11.5×10^{-3}	10×10^{-10}	7.44×10^{-3}	59×10^{-10}
Sugar Cane	2950.6	5.5×10^{-7}	32.2×10^{-3}	28×10^{-10}	20.98×10^{-3}	167×10^{-10}
Cucumbers	107.0	0.2×10^{-7}	1.1×10^{-3}	1×10^{-10}	0.72×10^{-3}	6×10^{-10}
Cantaloupes	214.0	0.4×10^{-7}	2.4×10^{-3}	2×10^{-10}	1.54×10^{-3}	12×10^{-10}
Watermelons	160.5	0.3×10^{-7}	1.7×10^{-3}	1×10^{-10}	1.12×10^{-3}	9×10^{-10}
Dry Peas	917.7	1.7×10^{-7}	10.0×10^{-3}	9×10^{-10}	6.40×10^{-3}	51×10^{-10}
English Peas	271.6	0.5×10^{-7}	2.9×10^{-3}	3×10^{-10}	1.86×10^{-3}	15×10^{-10}
Field Peas	271.6	0.5×10^{-7}	2.9×10^{-3}	3×10^{-10}	1.86×10^{-3}	15×10^{-10}
Commercial Applicators (all Crops)	1082.7	2.0×10^{-7}	11.8×10^{-3}	10×10^{-10}	7.82×10^{-3}	62×10^{-10}

Footnotes (Table 14)

a/ Exposure data from Table 3.

b/ Lifetime risks were estimated as follows:

$$\text{Risk Slope} \times \frac{\text{working lifetime (40 years)}}{\text{average lifetime (70 years)}} \times \frac{\text{Total Exposure (ug/year)}}{\text{365 days/year}} \times \frac{\text{1 person}}{\text{65 kg}} \times \frac{\text{1 mg}}{\text{1000 ug}}$$

c/ Trifluralin risk slope = 7.7 x 10^{-3}/mg/kg body weight/day.

d/ NDPA risk slope = 3.6/mg/kg body weight/day.

e/ C_7/C_8 risk slope was assumed to be as large as the diethylnitrosamine (DENA) risk slope of 33/mg/kg body weight/day.

This assumes an average working lifetime of 40 years, an average lifetime of 70 years and an average body weight of 65 kilograms.

Thus, for example, the lifetime individual risk (R) for a mixer/applicator/loader from exposure to trifluralin while treating soybeans is:

$$R = 7.7 \times 10^{-3} \times \frac{860.2}{365} \times \frac{40}{70} \times \frac{1}{65} \times \frac{1}{1000}$$

$$= 1.6 \times 7^{-10}$$

The risks for NDPA and C_7/C_8 nitrosamines (Tables 14) were similarly calculated (Regelman, 1981c), using the appropriate slopes as above, and using exposure data from Table 3.

The risks to mixer/applicator/loaders from exposure to trifluralin are in the order of 1×10^{-7} and range from 0.2×10^{-7} for "greens" to 5.55×10^{-7} for sugar cane. The range for NDPA is from 1×10^{-10} for okra, "greens", cucumbers, and watermelons to 28×10^{-10} for sugarcane. The range for C_7/C_8 nitrosamines is 1×10^{-10} for cucumbers to 167×10^{-10} for sugarcane.

b. Comparison of Risk Estimates with those of the PD 1/2/3.

The lifetime individual risk to mixer/applicator/loaders from exposure to the NDPA nitrosamine contamination in Treflan® was estimated in the PD 1/2/3 to range from 0.15×10^{-7} for "greens" and cucumbers to 4.60×10^{-7} for sugarcane. The estimates for nitrosamines (C_7/C_8) in this document (Table 14) range from 6×10^{-10} for okra, "greens", peppers, and cucumbers, 167×10^{-10} for sugarcane. (The range for NDPA nitrosamines risk is currently somewhat lower than that for the C_7/C_8 nitrosamines. It was deemed appropriate to compare the current highest nitrosamine range of risk figures, C_7/C_8, to those for NDPA in the PD 1/2/3.)

The current risk from exposure to nitrosamines is lower than that calculated in the PD 1/2/3 due to a reduction in NDPA contamination in Treflan® from a level of 5 ppm to an average of 0.10 ppm with the introduction of new methods employed in Elanco's manufacturing process. Also, as discussed, a different mathematical model was used to calculate the slope parameters in this document.

Based on Elanco's chronic feeding study, the risk from trifluralin itself is established as the major source of the risk associated with exposure to Treflan®. The largest lifetime individual cancer risk estimate from exposure to the trifluralin in Treflan for mixer/applicator/loaders is 5.5×10^{-7} for sugar cane. In the PD 1/2/3, the highest risk from exposure to Treflan® was 4.6×10^{-7} but it was due to the levels of NDPA contamination present in

Treflan® at that time. Similarly, in the PD 1/2/3, the risk to commercial applicators was 1.70×10^{-7}, whereas currently the highest risk to commercial applicators is 2.0×10^{-7} from exposure to the trifluralin in Treflan®. The risks due to the NDPA and C_7/C_8 nitrosamines do not add appreciably to the total risk currently associated with exposure to Treflan®; there would be no change in the order of magnitude. Thus, while the source of risk has changed from NDPA to trifluralin, the risk associated with mixer/applicator/loader exposure to Treflan® as calculated in the PD 1/2/3 has not changed significantly; the risk is of the same order of magnitude.

In order to account for the fact that mixer/applicator/loaders also are exposed to additional risk through their diet, one can add the two risks. When the total dietary risk is added to the highest worker risk for the PD 1/2/3, a figure of 49.3×10^{-8} is obtained (3.3×10^{-8} plus 46.0×10^{-8}). Similary, when the same computation is done with the current risk figures, a figure of 108×10^{-8} is obtained (53×10^{-8} plus 55×10^{-8}). This comparison shows that the risks associated with exposure of mixer/applicator/loaders to Treflan® have increased by a factor of 2. This is not considered to be an appreciable increase.

4. Reentry Risk

a. Nitrosamines

In the Air

Any risk associated with exposure to nitrosamines in air would be insignificant. The estimates for nitrosamine exposure in the air as a vapor were calculated for a few crops in the PD 1/2/3 and were found to be negligible; the risk was also assumed to be negligible. Mittleman (1978) stated that nitrosamine exposure in the air as particulate matter was also insignificant and, therefore, no risk estimates were calculated in the PD 1/2/3. Regelman (1981b) agreed that inhalational or dermal exposure to nitrosamines on particulate matter in the air was negligible; therefore, no risk estimates for exposure to nitrosamines in the air were calculated for this document, since current exposure to nitrosamines is lower by a factor of about 50 than it was at the time the PD 1/2/3 was issued.

In the Soil

The Agency had calculated in the PD 1/2/3 dermal exposure estimates for NDPA in the soil, since reentry exposure was theoretically possible, and arrived at a figure of 0.036 micrograms per year. However, this was considered to be only a theoretical estimate and not an actual estimate because, as stated in the PD 1/2/3, there is extreme variability in the type of field activities performed during reentry, in the degree of physical contact with the soil, in the amount of exposed body area, in the length of time exposed, and in the partition coefficient of trifluralin between the soil particles and the part of the human body which comes in contact with the soil particles. Because of the possibility of a high degree of inaccuracy, and because the exposure was expected to be low, if it existed at all, the Agency determined that it would not be reasonable to calculate a risk estimate for the PD 1/2/3 that might be incorrect by several orders of magnitude.

Dermal exposure to nitrosamines under reentry conditions was calculated for this document to be no greater than 5×10^{-6} micrograms per year for NDPA and 1×10^{-6} micrograms per year for C_7/C_8 nitrosamines. Because exposure estimates at these low levels are not reliable and because they are negligible amounts, the Agency assumed that any risk associated with exposure to nitrosamines in the soil would also be negligible.

b. Trifluralin

The Agency estimated reentry exposure to trifluralin as a vapor in Section II. B. The total trifluralin exposure during reentry, including inhalation and dermal contact with trifluralin vapor, and dermal contact with trifluralin adsorbed to particles in the soil (Table 9) was used to calculate the risk to workers reentering Treflan®-treated fields. The risk estimates for several crops are presented in Table 15.

The lifetime individual risks were calculated as described for the mixer/applicator/loaders, using a slope of 7.7×10^{-3} per mg/kg/body weight/day. The risk estimates range from 1.1×10^{-9} for cotton to 4.2×10^{-9} for tomatoes.

5. Summary of Dietary and Worker Risk

The magnitude of risk associated with a chemical depends on its potency as a carcinogen, as well as the extent to which the general public or workers are exposed to the chemical. If a certain chemical is highly carcinogenic as indicated by the slope parameter, but the exposure is very low, the risk may be acceptable if it is offset by the benefits derived from its uses. Conversely, if a chemical is a mild carcinogen, but exposure is extensive, the risk may not be acceptable if it is not offset by benefits.

For example, this document discusses risks associated with three chemicals, each with a different potency and different exposure. Trifluralin is the least potent of the three with a slope parameter of 7.7×10^{-3}, whereas NDPA is more potent (slope = 3.6), and C_7/C_8, assumed to be as carcinogenic as DENA, is the most potent (slope = 33). However, the two nitrosamines present a lower risk to the general population and to workers because, though their slopes are higher, their concentration in Treflan® is lower than 1 ppm, while trifluralin's concentration is 445,000 ppm (44.5 percent). The exposure to the nitrosamines is lower than exposure to trifluralin. Thus, the potential carcinogenic risk from exposure to Treflan® is now primarily due to trifluralin itself.

Table 15

Trifluralin Risk Estimates - Reentry[a/]

Crop	Total Trifluralin Exposure (micrograms per year)	Lifetime Individual Risk [b/][c/]
Soybeans	8.09	1.5×10^{-9}
Cotton	9.07	1.1×10^{-9}
Beans	8.76	1.6×10^{-9}
Tomatoes	22.88	4.2×10^{-9}
Trees/Vine	12.68	2.4×10^{-9}
Cole Crops	7.86	1.5×10^{-9}

[a/] Exposure data from Table 9.

[b/] Trifluralin slope = 7.7×10^{-3}(mg/kg body weight/day)$^{-1}$

[c/] Risks were calculated as described for mixer/applicator/loaders in Table 14.

In the PD 1/2/3, the total dietary risk associated with exposure to Treflan® was 3.3×10^{-8}. The highest mixer/applicator/loader risk was 4.60×10^{-7} for sugarcane and 1.70×10^{-7} for commercial applicators. Risk to reentry workers was highest for tree and vine crops at 2.1×10^{-8}, but reentry risk was considered negligible when photodegradation was taken into account. The risk at that time was due to exposure to the NDPA carcinogen contaminant. When the benefits of the use of Treflan® were assessed, the Agency determined that the benefits outweighed risks if certain recommendations were followed (PD 1/2/3).

In this document (PD 4), the highest total dietary risk associated with exposure to Treflan® is 5.3×10^{-7}. The highest mixer/applicator/loader risk is 5.5×10^{-7} and the highest reentry risk is 4.2×10^{-9}. These risks are associated with exposure to the trifluralin in Treflan®. There are some risks associated with the nitrosamines in Treflan®, but they are negligible when compared to those for trifluralin as discussed above. This is due to the large reductions which have already occurred in nitrosamine contamination levels.

A comparative summary of the risks in the PD 1/2/3 and this document is found in Table 16.

Currently, the dietary risk has increased by one order of magnitude, whereas mixer/applicator/loader risks have remained essentially the same. The highest reentry risk has decreased by one order of magnitude.

The overall risk has not changed significantly since the PD 1/2/3 was issued. The benefits, as discussed more fully in Section III. B., have varied slightly, but have not changed appreciably.

D. Ecological Effects

In the PD 1/2/3, the Agency indicated that trifluralin was highly resistant to leaching, was strongly adsorbed to organic matter, and did not readily run-off from treated fields. On this basis, the Agency determined that trifluralin did not meet or exceed the risk criteria for adverse ecological effects on aquatic oraganisms.

However, new information and reinterpretation of old data shows that trifluralin could reach aquatic environments through soil runoff. Trifluralin is persistent and may be further long lived when sediment bound residues fail to degrade and are slowly desorbed yielding low-level chronic exposures to aquatic populations. The desorption or disassociation of trifluralin from this "soil carrier" may be biologically significant (Touart, 1981). The very high toxicity of trifluralin to aquatic organisms is well established (Cope, 1966; Macek et al. 1969, 1976; Parrish, et al.1978). MATC (Maximum Acceptable Toxicant Concentration) levels for finfish are typically 1-5 ppb. Aquatic

Table 16

Summary of Risks Estimated in the PD 1/2/3 and PD 4

	PD 1/2/3[a]	PD 4[b]
Dietary (total)	3.3×10^{-8}	5.3×10^{-7}
Mixer/Applicator/ Loaders (Highest)	4.6×10^{-7}[c]	5.5×10^{-7}[c]
Reentry (Highest)	2.1×10^{-8}[d]	4.2×10^{-9}[e]

a/ Risk due to NDPA.

b/ Risk due to Trifluralin.

c/ The highest risk was associated with sugarcane treated with Treflan^R.

d/ The highest risk for NDPA vapor was associated with the tree/vine crop.

e/ The highest risk for trifluralin from vapor plus trifluralin from soil was associated with the tomato crop.

organisms also bioconcentrate trifluralin from 4000 - 150,000 times (Sanborn, 1974; Parrish et al., 1978). It is not known if this bioaccumulating tendency represents a biomagnifying problem or if any adverse effects are associated with a high trifluralin body burden. Additionally, Couch et al. (1979) have recently reported vertebral dysplasia in sheepshead minnows (Cyprinodon variegatus) exposed in early life stages to 5.5 ppb or greater trifluralin. A no effect level for this anomaly has not been reported.

The amount of trifluralin lost from treated fields in runoff as reported by several investigators has been summarized by Wauchope (1978). A maximum loss of 0.76 percent of the applied treatment to cotton plots has been reported with concentrations in runoff as high as 120 ppb (water plus suspended sediment) and 1.6 ppb (filtered water alone) documented (Sheets, 1972). Thus the Agency no longer considers the transport of trifluralin residues unlikely and the resulting aquatic concentrations of the herbicide insignificant.

On September 5, 1980, the Agency amended the registration for Treflan® EC to include use on field corn, sorghum, and barley under authority of FIFRA 3(c)(7)(B). The Agency stated (Mountfort, 1980) the labeling was acceptable since Elanco had agreed in part that "When required by the Agency, you will submit and/or cite the data pertaining to the movement and concentrations of trifluralin in the environment from typical application and data on the hazards to aquatic organisms. If the conditions of this amendment are not compiled with, the registration will be subject to cancellation in accordance with Section 6(e) of the Act."

Therefore, because trifluralin can be transported as bound residues in soil runoff, has been shown to be chronically toxic to fish at extremely low levels, and aquatic organisms have been shown to bioaccumulate trifluralin, the Agency has determined that a field monitoring study is necessary to assess possible adverse effects to these nontarget aquatic animals. The Agency still considers the hazard of trifluralin to terrestrial animals to be slight (Touart, 1981).

The requirement for the field monitoring study is being proposed not because RPAR criteria have been met or exceeded, but because the Agency has determined that information exists which indicates that possible adverse effects to aquatic animals could occur in bodies of water adjacent to Treflan®-treated fields.

III. Analysis of Comments

After the Notice of Determination was issued concerning the Treflan® RPAR on August 30, 1979, the Agency received comments from the Secretary of Agriculture, the Scientific Advisory Panel (SAP) and 17 other concerned individuals and organizations. Many of the respondents wrote to express their concurrence with the Agency's proposed decision: the Secretary of Agriculture [Appendix B], Merkle [30000/32:#2], Nalewaja [30000/32:#3], Jennings [30000/32:#4], Upchurch [30000/32:#5], Lange [30000/32:#7], Davis [30000/32:#14], Leggett [30000/32:#15], and Aves [30000/32:#16]. Other requested information which was subsequently supplied by the Agency: Kempen [30000/32:#1], Stanger [30000/32:#8], Teramura [30000/32:#9], Burr [30000/32:#10], Dart [30000/32:#11] and Baldi [30000/32:#13]. Three commenters disagreed with several portions of the Agency's position or rationale used to arrive at that position: Elanco [30000/32:#6], Knake (Intersociety Consortium for Plant Protection) [30000/32:#12], and American Cyanamid [30000/32:#17]. Since the comments on the PD 1/2/3 from the SAP [Appendix A] and these last three respondents are, for the most part, lengthy and detailed in nature, the responses are organized by topic and are discussed below. As indicated in the following discussion, some aspects of the PD 1/2/3 assessment of risks and regulatory requirements have been changed to reflect the recommendations of the SAP and others. Other aspects of the PD 1/2/3 remain unchanged.

A. Comments Relating to Risk

1. Worker Exposure

a. Exposure Estimate of N-nitrosodipropylamine (NDPA)

Knake [30000/32:#12] asked about the concentration which would result if one to two pints of trifluralin containing less than one part per million nitrosamine contaminant (NDPA) were mixed with a million pounds of soil. Additionally, he stated that if the Agency was concerned about applicator exposure, a few trips to the field to see actual use practices might have helped.

Agency scientists calculated that if the product in question was Treflan®, the resultant concentration of the nitrosamine contaminant would be 0.5 to 1×10^{-6} microgram/gram soil or 0.5 to 1 part per trillion, assuming a uniform distribution of nitrosamine throughout soil. This fact, however, has no impact on estimates of worker exposure during application, since the Agency estimates were based on residues of NDPA in air and dust samples collected during actual field experiments (Day et al., 1978). Concentrations of the nitrosamine NDPA in dust collected behind a spray rig applying Treflan® ranged from 0.01 to 0.07 microgram/gram or 10,000 to 70,000 parts per trillion. Knake's point regarding field trips is well taken. During the trifluralin review, field trips by Agency scientists and other staff members were undertaken as were consultations and discussions with applicators, USDA representatives, University representatives and registrants. The information obtained was applied to the Agency's estimates of risk outlined in the PD 1/2/3. Thus, the above comment [30000/32:#12] does not alter the worker exposure estimates calculated by the Agency and presented in the PD 1/2/3.

b. Mixer/Applicator/Loader Exposure to NDPA

1) Inhalation

Elanco [30000/32:#6] stated that the EPA estimate of exposure to NDPA via inhalation of dust was excessive by about 13.5 times the median value measured by the company under field conditions (Day et al., 1978).

Elanco in a subsequent submission (Elanco, 1980c) objected to the Agency's use of the mean of four vacuum sweeper samples (96×10^{-6} ug NDPA/m^3) in its applicator/mixer/loader inhalation exposure estimates.[3] Instead, Elanco suggested that data from the dust pans[4] should have been included as well. In addition, Elanco "fuzzed-over" (their term) data from four other experiments[5] (data which were totally excluded as invalid in the Agency's evaluation), including them in a Log-Probit statistical treatment using all the data from the vacuum sweeper and dust pan samples.

As a result, Elanco estimated that dust-NDPA levels were actually 7.3×10^{-6} ug/m^3, about 13.5 times lower than the Agency's figure of 96×10^{-6} ug/m^3. The Agency's decision to use only the valid vacuum sweeper data[3] rather than the dust pan samples and the results of invalid samples[5] was based on the following rationale (Regelman, 1981b).

a) In their original submission (Day et al., 1978) Elanco reported that they collected large dust samples in their field monitoring study to provide a basis for determining the concentration of trifluralin and NDPA on particulate matter in the air breathed by mixer/applicator/loaders. The particulate samplers collected large samples of dust with the concentrations of the chemicals being higher on the dust from the vacuum sweeper (VC) than from the dust pans (DP).

3/ Day et al., 1978, Experiments # DMS 7-3VC, DMS 7-4VC, DMS 7-5 VC, and DMS 7-6VC.

4/ Day et al., 1978, Experiments # DMS7-3 DP1, DMS 7-3 DP2, DMS 7-4 DP1, DMS 7-4 DP2, DMS 7-5 DP, and DMS 7-6 DP.

5/ Day et al., 1978, Experiment # DMS 7-7 DP1, DMS 7-7 DP 2, DMS 7-7 VC 1, and DMS7-7 VC 2.

They stated this was due most probably to the smaller sized particles (0.5u - 10u) collected by the VC. They stated that theoretically only the respirable particulates should reach the lungs, but larger dust particles could be deposited in the nasal passages. Elanco then used the chemical content of the VC dust samples (presumably more representative of respirable particles) to calculate the "...maximum exposure to NDPA and trifluralin via inhalable particles." The results were set out in Table IV-15 of their submission, with exposure estimates given for both respirable and total particulates. The Agency agreed that this approach was valid and that using the data from the VC samples would give a reasonable estimate of typical inhalational exposure. The Agency used these figures in the exposure estimate set forth in the PD 1/2/3.

Elanco in their additional comments on the PD 1/2/3 submitted September 4, 1980, (Elanco, 1980c) proposed that the data on the chemical content of the dust pan samples should also be included. However, in their original submission, they chose not to incorporate these data into their inhalational exposure estimate because of the reasons described above.

b) The larger particle DP samples contained lower levels of trifluralin (and NDPA and C_7/C_8 nitrosamines) than the VC samples, presumably due to their lower surface-to-volume ratio. This presumption is supported by a comparison of the means of the two data sets, in which the VC samples appear to contain nearly three times the average concentration of NDPA as the DP samples (96×10^{-6} vs. 36×10^{-36} ug/m^3). Since the particle-size distributions were apparently quite different in the two groups, it would seem inappropriate to average all reported data. Instead, the VC samples (which were more representative of respirable particles) were used exclusively by the Agency and initially by Elanco to estimate maximum exposure to inhalable particles. The average of 96×10^{-6} micrograms per cubic meter was based on four measurements from experiments in which Treflan® application and incorporation operations were carried out simultaneously. The Agency used this approach in the PD 1/2/3 and still deems it valid.

c) Elanco's rationale for using the log-probit technique to evaluate this group of data is unclear from their rebuttal comments. The Agency does not agree that Elanco has proven that the VC data are "skewed", or that, a log/probit analysis is justified.

d) We do not understand the justification for "fuzzing-over" data (i.e. including data in the "count" of the number of samples, but not including the specific values in the correlation computation). It is the Agency's understanding that these "fuzzed-over" data[37] were collected under application/incorporation conditions quite different from those of the other data; i.e., applications and incorporation of Treflan® were carried out separately. Thus, those measurements do not reflect total particulate phase exposure during simultaneous application and incorporation (Day et al., 1978, page 5).

e) The Agency could have taken the conservative approach that the highest measured VC sample (296×10^{-6} ug NDPA/m^3) was more representative than the mean of that group of data. The Agency's estimates would than have been three times higher than actually computed.

f) Finally, there were only four valid VC data points. Considering this limited amount of data, the Agency determined that averaging them was the best possible approach.

2) Dermal

Elanco also suggested [30000/32:#6] that the EPA estimate of dermal exposure based on a single positive result in a cloth charcoal adsorber sample was excessive and that alternative estimates submitted by them reduce this dermal exposure to one-sixth that calculated by EPA.

The EPA estimate of dermal exposure was based on an unsatisfactory data base since experiments designed to measure potential dermal exposure were unsuccessful. Attempts were made by Day et al. (1978) to determine dermal exposure to the applicator by analysis of cotton gauze arm pads, cotton shirts, and cotton gloves worn by the applicator. These studies, however, were not useful in predicting dermal exposure due to the extremely poor recoveries of NDPA and trifluralin from samples innoculated in the field, contamination of field "blanks", and the inability of the cloth material to prevent dissipation of NDPA and trifluralin during the work day (Mittelman, 1978).

In recognition of these difficulties, Day et al. attempted to simulate dermal exposure by constructing an "adsorber" consisting of a layer of charcoal held fast around a glass jar by a tightly bound cotton cloth. Only one study using the charcoal-cloth adsorber revealed positive levels of NDPA in the charcoal. The Agency considered this to be a valid measurement and based the estimate of dermal exposure in the PD 1/2/3 on this value.

Elanco (1980c) stated that the negative results for NDPA measurements from the experiments using the cotton gauze arm pads, cotton shirts, and cotton gloves can be used. They calculated the maximum levels of NDPA that could have been there by using the limit of sensitivity of their method of detection. Using these levels, the average dermal exposure is 0.0138 ug/hr, a figure one sixth that of the EPA's figure of 0.083 ug/hr.

The Agency maintains that the studies using cotton gauze arm pads, cotton shirts, and cotton gloves are not useful in predicting dermal exposure and that the measurement derived from the study using the charcoal-cloth adsorber is the appropriate figure to use. The Agency agrees that the resultant exposure estimate is clearly biased toward conservatism, but in the absence of adequate data, no alternative action was deemed appropriate (Mittelman, 1980). The

Agency assumes that dermal exposure can occur at least up to the one level measured in the field study (Day et al., 1978). Currently, however, the average NDPA contamination in Treflan is approximately 1/50 of the level present when the PD 1/2/3 was issued. The revised exposure estimate outlined in Section II.B. of this document takes this into account.

c. Reentry Field worker exposure

Elanco [30000/32:#6] asserted that there is no evidence nor is it reasonable to assume that field workers who reenter trifluralin-treated fields are exposed to NDPA; that EPA inhalational exposure estimates were as much as 100 times too high. Elanco also criticized EPA's use of laboratory results instead of field studies indicating negligible exposure.

Elanco (1980c) further explained that they used results from a study by White et al. (1977) which measured trifluralin volatilization loss under field conditions. NDPA was not measured because it would have been below the level of detection. Elanco calculated the theoretical levels of NDPA that would have been present by using a trifluralin to NDPA ratio of 89000:1, a ratio which they criticized EPA for using in the dietary exposure estimate presented in the PD 1/2/3. (Elanco's comment is further discussed in Section III. A. 2. of this document).

Using these theoretical NDPA levels as a basis for calculation, Elanco compared their inhalational exposure estimates with those presented by EPA in the PD 1/2/3 and found the EPA values to be about 100 times too high. They presented a comparison of Mittelman's (1978) and Elanco's calculations shown in Table 17.

Table 17

NDPA Innalation Exposure (ug/year)[1/]

Crop	Mittelman	Elanco	Ratio
Beans	3.0	0.024	125:1
Tomatoes	5.0	0.068	74:1
Tree and Vines	15.0	0.145	103:1
Cole Crops	6.0	0.077	78:1

1/ Elanco, 1980c.

The Agency might have used such an approach if no data were available to allow the derivation of a more appropriate model for the estimation of inhalationalexposure. The inhalation exposure estimates reported in the PD 1/2/3 were based on actual field measurements (Day et al., 1978) in conjunction with a laboratory model system (Oliver, 1978) as described by Mittelman (1978, Addendum 5). Since this approach was based on actual NDPA measurements from both field and laboratory experiments, it was considered to be a better model than that used by Elanco in calculating theoretical levels of NDPA.

The Agency affirms that its field/laboratory model affords a more realistic estimate. Both methods (Elanco's and the Agency's) arrive at estimates of exposure for inhalation which do not pose a significant carcinogenic risk. The risk calculated from the Agency's exposure figures was outweighed by the benefits of trifluralin use, as the risk would be if calculated from Elanco's estimates. Currently, the risk would be even less than that calculated by the Agency for the PD 1/2/3 primarily since NDPA contamination is currently much less than it was previously estimated to be, as discussed in section II. B. 3. of this document. The Agency concluded in the PD 1/2/3 that inhalational exposure and risk under reentry conditions were negligible, and presently reaffirms that conclusion. If Elanco's model were used to calculate NDPA exposure, it too would be negligible; there would be no change, therefore, in the Agency's regulatory position if either model were adopted.

The "worst-case" EPA estimate of dermal exposure was also criticized by Elanco [30000/32:#6] as being exaggerated, since it suggested that a worker would collect nearly two pounds of soil on his exposed skin.

The EPA estimate of dermal exposure to reentry workers based on contact with NDPA contaminated dust was presented for illustrative purposes to indicate that dermal NDPA exposure during reentry is theoretically possible. Since no reentry dermal exposure data exist, it was considered appropriate to determine the "worst-case" situation, i.e.,the worker is literally covered with dust. The Agency used this approach only to describe an upper limit to possible exposure.

The EPA dermal exposure estimate was based on the assumptions that a worker entering the field has a total uncovered skin surface area of 2,900 cm^2 and that a uniform layer of soil forms a 1.0 mm thick film on the uncovered skin and that there are 3 x 10^6 grams of soil per cubic meter. Using these assumptions, the quantity of soil on the exposed skin would be 0.87 kg or almost 2 lbs.

Currently, however, the Agency is using a different method to estimate the amount of dust a worker could collect on his skin (Jensen, 1981). This approach was used in the revision of the exposure estimates discussed in Section II. B. 3. of this document. It was estimated that a worker could collect approximately four grams of dust on his exposed skin, rather than two pounds as originally calculated in the PD 1/2/3.

As discussed in Section II. B. 3. of this document, the exposure to NDPA at current contamination levels in Treflan© was calculated to be 5 x 10^{-6} micrograms per year, a level judged to be negligible. No risk was calculated for this exposure, since the risk would also be assumed to be negligible; photodegradation, soil metabolism, other degradative and metabolic pathways, and dermal penetration of 22 percent would result in even lower levels of exposure than that calculated.

2. Dietary Exposure

Elanco stated that "There is no evidence, or is it reasonable to assume, that there is any dietary exposure to NDPA as a result of the use of Treflan" [30000/32:#6].

In its PD 1/2/3 the Agency acknowledged that West and Day (1977) could not detect NDPA at a test sensitivity of 0.1 to 0.2 ppb in crops grown in agricultural land treated for successive years with Treflan® EC containing as much as 450 ppm NDPA.

However, the Agency reviewed laboratory studies which indicate that nitrosamines can be taken up into plants grown in ^{14}C-NDPA treated soils over at least 49 days (Dean-Raymond and Alexander, 1976; Berard, 1977; Berard and Rainey, 1977). From levels reported in these studies and those of West and Day (1977) the Agency concludes that it is reasonable to assume that NDPA could be found in various Treflan© treated commodities at or above the test sensitivity of 0.1 ppb (Donoso, 1980). Because of this the Agency felt it was prudent to develop the dietary exposure case described in the PD 1/2/3 on trifluralin.

Elanco further stated that it considered two of the Agency's assumptions used in the dietary exposure estimate to be unsound:

- That trifluralin residues up to and including the established tolerance limit are "probable."
- That NDPA residues in crops will be in the same ratio to trifluralin as that observed in the formulation. (Elanco, however, used the same ratio of 89,000:1 when they calculated inhalation exposure to NDPA as shown in section III. A. 1. c. of this document discussing field worker exposure.)

Elanco further stated that the FDA and others have analyzed over 20,000 samples covering more than 27 crops in which no detectable trifluralin residues were found at a detection limit of 0.01 ppm.

Though many such surveys have failed to detect trifluralin residues in crop samples, FDA has found trifluralin residues in commodity samples on a number of occasions in its surveillance and compliance programs. This was indicated in the trifluralin PD 1/2/3. The Agency, however, did not consider these data sufficient to be used in its dietary exposure estimate because the number of positive findings were few and ill-defined; nine samples were identified as "raw agricultural products", miscellaneous items", and "fish and marine animals".

The Agency developed a "worst case" exposure in the PD 1/2/3 based on information on the percentage of crop acreage treated, published information on trifluralin tolerances, data on food factors, and a then-established trifluralin to NDPA ratio of 89,000:1 in formulated Treflan®. Using the assumption that it was possible that trifluralin could be present at its tolerance levels, the Agency calculated in the PD 1/2/3 the "Potential Dietary Exposure to NDPA" and determined, using the above published information, that the total probable dietary exposure to NDPA would be about 1.92×10^{-9} mg/kg body weight/day. The Agency stated in the PD 1/2/3 that these residues may in fact be much lower. The Agency's dietary carcinogenic risk estimate based on those exposure figures represented the "worst case".

Elanco offered alternative estimates of dietary exposure to NDPA associated with use of trifluralin [30000/32:#6]. One such estimate was further explained in a letter from Elanco (Day, 1980). The estimates were extrapolated from study results of trifluralin residues in crops performed by Elanco. Trifluralin residues used were either the highest level reported or the sensitivity of analytical methods for trifluralin that were used. It was shown that the total dietary risk based on those NDPA exposure estimates was 8.05×10^{-9}, based on exposure to Treflan® containing 5 ppm NDPA.

Because of the acquisition of new data on the carcinogenicity of trifluralin itself and because a new exposure estimate was needed, the Agency decided to base the new exposure estimate on actual residue data submitted over the years by Elanco on the several crops expected to contain trifluralin and nitrosamine residues (Regelman, 1981a). It was determined that because Treflan® had been shown to contain two chemicals (trifluralin and nitrosamines, including NDPA and C_7/C_8) shown to be associated with tumor production in laboratory animals, it would be more appropriate to arrive at an estimate more closely approximating "real world" conditions. The Agency determined that it would be reasonable to use these residue studies for the exposure estimate as they comprised a large data base which was not highly variable.

It was assumed the data were representative of treated crops generally. A discussion of dietary exposure to trifluralin and nitrosamines was presented in section II. B. 1. of this document. The total dietary risk calculated by the Agency (Section II. C. 2 for NDPA was 5.85×10^{-11}, less than that calculated by Elanco (Day, 1980), because the Agency's estimate is based on 0.1 ppm NDPA in Treflan® instead of 5 ppm. The total dietary risk calculated for trifluralin by the Agency was 5.3×10^{-7}, the highest per crop being 2.2×10^{-7} for carrots. The Agency's calculations for C_7/C_8 nitrosamine total dietary risk was 1.03×10^{-10} and does not contribute significantly to the overall risk. These estimates, because they are based on actual trifluralin residue data, reflect more closely the actual concentrations of the three chemicals in the diet than a "worst case" (theoretical maximum) estimate would.

3. Toxicology

a. Cancer Risk Assessment

1. Elanco's Comments

Elanco [30000/32:#6] stated: "The cancer risk assessment was determined by the use of questionable methods..... Elanco cannot accept the model used by EPA to extrapolate from results in published animal studies. The model is apparently intended to be a generalization of the familiar one-hit exponential model. However, it can be demonstrated that the particular form of the model used by EPA is invalid when tested against actual data. It can also be shown that the methods of calculation based on the unique form of the model lead to erroneous slope estimates. Since linear risk extrapolation relies on such estimates, all risk assessments made by EPA must be considered invalid. Elanco recognizes that the entire subject of risk assessment is in a state of flux, and that objections may legitimately be raised to all approaches. However, the extrapolation procedures used previously by EPA in the decision document supporting the denial of the petition to suspend the registration of Treflan® (Federal Register, August 8, 1977) come far closer to acceptability than the method used in the present case."

Elanco submitted additional comments (Elanco, 1980c) explaining more fully the reasoning behind their position. They had specific suggestions for calculating the risk assessment using a model which they claimed would fit the NDPA data better and give a more precise estimate of risk.

The Agency's Carcinogen Assessment Group (CAG) reviewed Elanco's comments (Chen and Haberman, 1981). The CAG stated that Elanco's main criticism was that the Agency's "one-hit" model, $P = 1 - \exp(-bdt^m)$, determined by using the Druckrey relationship, $(t_{50})^n \times d = \text{constant}$, may not adequately represent the real dose-response curve at time points other than t_{50}. Based on the cumulative tumor incidence in the highest dose group (out of nine dose groups) from the study by Druckrey et al. (1967), Elanco demonstrated that the model constructed by the Agency did not adequately fit the DENA data because the model overestimated the cancer incidence at early ages and underestimated the cancer incidence at later ages (e.g., the observed incidence was 100 percent at 760 days after correcting for mortality while the Agency's model predicted only 65 percent).

While Elanco's point is correct, it is not directly relevant to the Agency's risk assessment for NDPA (or DENA) because the Agency made no attempt to estimate the time course of tumor formation using its "one-hit" model and/or estimate the lifetime risk at high doses as Elanco had done. Instead, the Agency used Druckrey's potency parameter, $k = d(t_{50})^n$, solely to determine the potency parameter b when t = 1 (lifetime). The slope of the "one-hit" model, b, was intended to be used only for estimating lifetime risk at low doses. The Agency realizes that determination of the slope, b, which is intended for use at low doses, may be inaccurate for estimating risk at high doses, and that this procedure may incorrectly equate the value of n in Druckrey's formulation with the value of m in the "one-hit" model. However, the procedure was used because of the Agency's desire to estimate the slope for a large number of N-nitroso compounds from Druckrey's data, which are available only in the form of tabulated values of k and n. This procedure appeared to be the only method one could use to obtain a solution.

However, even though this assumption may be suspect, at least in the situations where it can be independently verified, its use does not appear to have introduced much error. For DENA and NDPA, where both tumor incidence data and Druckrey's parameters exist, the Agency's procedure used in the PD 1/2/3 does not differ appreciably from the multistage procedure which the Agency currently uses.

The carcinogenic potency of NDPA using the Druckrey index is estimated as 4.38 $(mg/kg/day)^{-1}$ which is close to 3.62 as estimated by the multistage model. It should be noted that the NDPA slope (potency) estimated by the Agency in the PD 1/2/3 of 0.4 $(ppm)^{-1}$ differs from 4.38 because it was assumed that ppm dietary consumption is equivalent between humans and animals. The Agency currently finds that this is not justified since the calories/kg of food is very different in the diet of man compared to laboratory animals, primarily due to the moisture content difference. The current procedure used is as follows: the ppm dose in animals is converted to mg/kg/day; this is then converted to mg/kg/day for humans to obtain the actual equivalent dose for humans.

The carcinogenic potency of DENA using the Druckrey index is estimated as 43.46 $(mg/kg/day)^{-1}$ which is again very close to 33.45 as estimated by the multistage model for C_7/C_8 nitrosamines.

These models (the "one-hit" and "multistage") are considered to be relevant only at low doses and may not fit at high doses, as the following example using the multistage model shows. Without converting to human equivalent dose, the carcinogenic potency of DENA for animals is $q_1^* = 5.72\ (mg/kg/day)^{-1}$, using the multistage model. Although the lifetime cancer risk at low doses is approximated by $P(d) = 1 - \exp(-5.72 \times d)$, (where d = dose), this formula is not applicable at high doses. For instance, one can not use this formula to calculate the risk at d = 0.15 mg/kg/day as Elanco had done. If the formula were used at d = 0.15, the risk would be only 0.58 instead of being 27/30 or 0.90 as observed. The risk predicted by the multistage model (when the full model is used) at d = 0.15 is 0.89 which closely agrees with the observed incidence of 0.90.

Therefore, the fact that CAG's procedure ("one-hit" model) does not fit well with Druckery's time-to-tumor data in the highest tested dose group does not necessarily imply that the method is invalid at low doses.

The dietary and worker risks associated with exposure to NDPA were recalculated using the multistage model and are described in Section II. C. along with the calculations for trifluralin and C_7/C_8 nitrosamines.

2) American Cyanamid's Comments

American Cyanamid, the registrant for Prowl®, an alternative herbicide for some trifluralin uses, commented verbally in April, 1980, to the Agency that the assumptions used in arriving at the carcinogenic risk estimate for the N-nitroso contaminant of Prowl® were not the same as those used for the N-nitroso contaminant of trifluralin. They requested that the NDPA/trifluralin carcinogenic risk be recalculated,using the same assumptions. The previous inhalation estimates in the PD 1/2/3 were based upon an assumed breathing rate for workers of 1.2 cubic meters per hour. This assumption has been changed to 1.8 cubic meters per hour to correspond to the breathing rate assumed in more current risk estimates calculated by the Agency for the types of work performed by mixer/applicator/loaders and field workers.

The new estimates for inhalational exposure were obtained by multiplying the previous exposure estimates in the PD 1/2/3 by 1.5. This was done because a breathing rate of 1.8 cubic meters per hour represents a 50 percent increase over the previous assumption of 1.2 cu m/hr. This was discussed in section II.B. of this document.

The risk to workers was then calculated and is presented in Section II. C. of this document. The estimates of the lifetime individual risk for mixer/applicator/loaders for NDPA presented in the PD 1/2/3 ranged from 0.15×10^{-7} to 4.6×10^{-7}. The new estimates range from 1×10^{-10} to 28×10^{-10}. The new estimates are two orders of magnitude lower, principally because of decreased NDPA contamination levels currently in Treflan®.

b. NDPA Oncogenic and Mutagenic Risk

The Agency asked the SAP to comment on the determination that low risks from DNA and gene effects are associated with the NDPA contaminant in Treflan®. The SAP (Appendix A, October 15, 1979) agreed with the Agency on this issue and agreed with the Agency's rationale for attributing the oncogenic risk of the trifluralin product to its NDPA contaminant at that time. The SAP also deemed as reasonable the Agency's assertion of lower risk at 1 ppm NDPA contamination than at 5 ppm, but stated that this assumption would have to be confirmed by the ongoing oncogenic study with the current Treflan® product containing levels of less than 1 ppm NDPA.

The results of this study were not available at that time. As discussed previously in this document, this study demonstrated that trifluralin itself, essentially free of NDPA contamination, is associated with the production of tumors in laboratory animals when administered in high doses.

The Agency reaffirms its position as discussed in the PD 1/2/3 that the mutagenic risks for DNA/gene effects from NDPA currently associated with trifluralin products would be low. However, the Agency and the SAP are also in agreement that this must be verified by properly designed mammalian studies, not currently available. The registrants will be required to conduct studies to assess these potential toxic effects.

c. Spindle Effects

On the basis of published studies, the Agency concluded in the PD 1/2/3 that trifuralin interferes with the spindle apparatus in dividing plant and animal cells and would thus have the potential to cause abnormal segregation of chromosomes. Elanco [30000/32:#6] asserted that "trifuralin is not a spindle poison in mammalian species...." and "... definitive studies show that trifuralin is very selective in its interaction with the microtubular protein of plant cells and that the compound does not react with mammalian microtubular protein." The Agency had expressed concern about trifluralin's potential to exert a "spindle effect" in mammalian cells because of its reported mode of action in plants. Elanco submitted a review article (Hess, 1979a) and three studies (Hess and Bayer, 1974; Hess and Bayer, 1977; and Hess, 1979b) on trifluralin's mode of action. On the basis of these studies, Elanco maintained that "trifluralin does not disrupt cell division processes or any spindle process when tested in vivo in animal cells."

The Agency disagrees with Elanco's position regarding the lack of trifluralin induced disturbances in the formation or the function of the cell division spindle in mammals (Mauer, 1980). Although studies are available delineating the probable mode of action of trifluralin in plant cells (consistent with its efficacy as a herbicide), insufficient or inconclusive evidence exists to exclude a comparable effect on the mitotic spindle (microtubular assembly) in mammals; in fact, there are animals studies suggesting such an interaction (Robinson and Herzog, 1977).

Furthermore, as an evolutionary conservative cell organelle, the apparatus for cell division does not differ significantly between plants and animals; hence similar spindle effects might be expected to occur in mammals exposed to trifluralin.

Regarding the first part of Elanco's objection ("spindle poison"), the Agency has already presented evidence for disruption of the cellular spindle apparatus in both (nontarget) plants and animals (PD 1/2/3). Although the studies were not well documented (e.g., as to levels of the NPDA contaminant), demonstration of trifluralin's ability to interfere with the formation or function of the microtubular elements of the cell division spindle was clearly illustrated at rather low "dosages" in three species of plants (at concentrations of 0.1 thru 1.6 ppb), as well as in two species of salamanders (10^{-4} to 10^{-5}M).

Further, in an extended series of studies in *Drosophila*, the continuous feeding of larvae at levels of 0.01 and 0.10 percent of a trifluralin preparation containing 177 ppm NDPA has consistently given evidence of nondisjunction as discussed in the PD 1/2/3 and subsequently by Murnik (1979). A repeat study by the same investigator with "pure" trifluralin (i.e., no detectable NDPA) was negative, however. Thus, although these limited animal studies may be considered inconclusive, they do suggest that high concentrations of trifluralin products (with or without stated levels of NDPA) have the capacity to disrupt the mitotic spindle in dividing animal cells, and thereby have the potential to cause abnormal segregation of chromosomes (nondisjunction) (Mauer, 1980).

As to the second Elanco contention ("selective action on plant microtubular protein"), three components can be identified: (1) binding of trifluralin to tubulin protein sub-units, which normally polymerize into microtubules to constitute the cyto-architectural elements of the cell division spindle (among other cellular processes); (2) assumed chemically-induced prevention (or inhibition) of such microtubular assembly and/or function; and (3) disruption of the cell division process and other spindle processes *in vivo* in animal cells (e.g., orientation).

In a series of published studies in plant cells (cotton, wheat, corn, etc.), trifluralin has been shown to bind specifically to plant tubulin, thus preventing the appearance of microtubular elements of the cell division spindle (Hess, 1979b; Hess and Bayer, 1974; Hess and Bayer, 1977; Bartels and Hilton, 1973 and 1974). In contrast, the same investigators reported no binding to pig brain tubulin *in vitro* nor any inhibition of polymerization into microtubules in these preparations at the aqueous saturated concentration (1 u M). Further, at supersaturated concentrations (1 to 10 u M) trifluralin apparently had no effect on the cell division of normal or transformed (XSFL-2) monolayer cell cultures of sheep lung, nor on cleavage of fertilized sea urchin eggs (Hess and Bayer, 1977).

The mode of action of trifluralin on tubulin and microtubular assembly has been compared to that of the well-known spindle poison, colchicine. However, there are differences in the pharmacological responses between these chemicals which have led some investigators to suggest essential chemical differences exist between plant and animal tubulin. For example, at least 1000 times as much colchicine as trifluralin was required to completely prevent microtubular formation in the alga, Chlamydomonas (2.5 - 3.75 mM vs. 3.75 - 5.0 u M; comparable no effect concentration levels were 0.25 mM and 0.1 u M, respectively). Similarly, mitotic disruption in wheat root tip cells and cultured blood lily endosperm cells occurred with 1.0 and 0.3 u M trifluralin, respectively, compared to 2.5 and 0.1 mM colchicine (Hess, 1979b). In contrast, 0.1 u M colchicine appears to be sufficient to disrupt cell division in HeLa cells (Hess, 1979b), as well to bind to pig brain tubulin preparations as per L. Wilson (SAP, October 9-10, 1979), whereas as noted above, supersaturated aqueous as per concentrations of trifluralin (up to 10 u M) appear to be inactive in certain animal cell systems. It has also been suggested that different binding sites for colchicine and trifluralin are involved which might also contribute to the presumed differences between plant and animal tubulin, and thus the differential responses (Hess and Bayer, 1976).

Trifluralin's inability to affect animal microtubules, however, may only be apparent, since, in the studies cited above, the chemical was generally tested only to the limit of its aqueous solubility. Other recent animal studies have reported effects on microtubular formation at aqueous (< 1 u M) as well as at supersaturated concentrations (greater than 10 u M). For example, microtubule oral band formation was delayed by 0.2 u M trifluralin in the large ciliate, *Stentor coeruleus* (Banerjee et al., 1975), while polymerization of purified pig brain tubulin into microtubules was prevented by concentrations of about 10 u M and above (Robinson and Herzog, 1977).

Hence, the animal studies cited in the Elanco rebuttal are insufficient and/or inconclusive to exclude possible interference with the mammalian cell division spindle *in vivo* (Mauer, 1980). In terms of the magnitude of any risk from spindle effect, the Agency has concluded the evidence is inadequate, since, (i) there are no valid *in vivo* mammalian studies, somatic or germinal, and (ii) it is not clear whether it is trifluralin itself, a metabolite, or a contaminant that is active. The SAP agreed with the Agency's proposed position requiring additional testing to clarify these uncertainties.

d. Spindle Effects Threshold

The SAP commented, "A threshold (does) exist(s) for spindle effects from compounds such as colchicine." (The inference is that this is true for other spindle inhibitors such as trifluralin.)

The SAP (Appendix A, November 30, 1979) based its opinion on the kinetics of the affinity for the same tubulin binding site of colchicine and benomyl, another chemical capable of interfering with the cell division spindle, and the resulting inhibition of polymerization of tubulin to microtubules. The Panel's opinion was strengthened by studies with mammalian cells it cited (referenced in the SAP submission as: Cox and Puck, 1969; Wilson, Anderson, and Chen, 1976) using the other well-known anti-mitotic agents, colcemid and the vinca alkaloids, as well as by a mouse micronucleus test with benomyl (referenced in the SAP submission as Seiler, 1977), all suggesting a threshold for spindle effects.

The Agency disagrees with the opinion expressed by the SAP (Mauer, 1980). A threshold for spindle effects and nondisjunction cannot be unequivocally demonstrated by the studies cited for either the antimitotic alkaloids, nor for benomyl. The *in vitro* studies (Cox and Puck, 1969; Wilson, Anderson, and Chen, 1976) were conducted with cell lines (CHO, EHB) displaying inconstant chromosome numbers; unsynchronized cell populations were treated; and no control cell clones were isolated for comparison to the treated isolates. The dose range between the concentration of agent needed to block movement of single chromosomes and that needed to cause complete mitotic arrest is extremely narrow (e.g., in the case of colcemid, 0.015 ug/ml and 0.03 ug/ml). Any reference to a mechanism involving what relative percentage of tubulin must be bound to account for selective inhibition of polymerization leading to "non-disjunction" is tenuous. Only 3 percent of cellular tubulin bound appears to be critical to block the entire spindle thus leading to polyploidy. Cellular tubulin is involved as well in cellular processes other than the mitotic spindle. There is no suggestion for thresholds involved in these processes.

The *in vivo* study cited (Seiler, 1977) was actually performed with methyl benzimidazole carbamate (MBC), the principle (active) metabolite of benomyl. The author reported no effect (no micronuclei) of MBC given orally to mice at a (single) dose of 50 mg/kg corresponding to a blood level of 8 ug /ml (the solubility limit of the compound). Further, the inference of a threshold for spindle effects (microtubular) was drawn by the investigator from his *in vitro* experiments with isolated pig brain preparations, in which 5 x 10^{-5}M (approximately 10 ug /ml) was the minimal effect level (25% inhibition of tubulin association), while 10^{-4}M (12 ug/ml) gave maximum effect (100% inhibition). Finally, the micronucleated erythrocytes which are counted as the end-effect in this test are not exclusively the product of spindle inhibition; micronuclei also occur following treatment with chromosome breakers. No effect levels one fifth to one tenth those for micronuclei have been reported with benomyl/MBC for reproductive effects in rats at 7.5 mg/kg, only a portion of which may be attributable to the chemical's effects on tubulin. Hence, the circulating threshold may conceivably be <8 ug /ml for these effects.

There are no comparable data available on the effects of trifluralin which could be related to a threshold. Although benomyl (MBC) and colchicine may have the same tubulin binding site, evidence is available that trifluralin does not share the same site (Hess and Bayer, 1976).

B. Comments Relating to Benefits

Elanco [30000/32:#6] alleged that EPA greatly underestimated the economic impact from the cancellation of Treflan®; that the economic loss would be significantly greater if current information relative to the planted acreage and the price of the agricultural commodities were used.

1. Base Planted Acres

The EPA analysis in the PD 1/2/3 used data which represented the most current information available on acreage at that time. Normally the Agency uses an average for the most recent three to five years; generally, this method is a good indicator of a "typical" production year after a hypothetical cancellation. To project acreage into the future is imprecise and is not normally undertaken in an analysis of this sort (Gaede, 1980a).

The 1974-1976 average number of planted acres was used as the analytical base for all trifluralin use sites other than cotton. A 1971-1976 average was used for cotton since the unusually low acreage for 1975 would have biased the three year average downward excessively.

The Agency has obtained more current data and finds that changes have occurred (Gaede, 1980b). The original EPA/USDA estimate of the percentage of planted soybean acres treated with trifluralin was approximately 10 percentage points lower than more current 1979 estimates; in addition, the EPA/USDA estimate of the percentage of planted cotton acres treated with trifluralin was approximately 10 percentage points higher than more current estimates. Deviations from the estimate are expected from an analysis that was not intended to represent any one specific year. Thus, unless drastic structural changes occur in U.S. agriculture, the estimate will probably be representative. Such changes could not be anticipated at the time of the analysis nor can they now be projected precisely (Gaede, 1980a).

2. Base Commodity Price

The Elanco contention of a downward bias in agricultural commodity prices is inaccurate. The same logic used in the estimating procedure for base acres was also used for commodity prices. The results of the analysis were stated in constant dollars (absent the influences of inflation, etc.) that corresponded to the years used for acreage data as stated in footnote 17 of the PD 1/2/3 (Gaede, 1980a).

The Agency concludes that the Elanco contention of bias associated with both base harvested acres and commodity prices is inaccurate. The EPA/USDA economic assessment was undertaken with the best available information provided by experts in relevant professions. This assessment is deemed appropriate as it now stands.

3. Relative Importance of Prowl® as a Treflan© Alternative

The American Cyanamid Company [30000/32:#17], proposed to "...bring the Agency's attention to errors in the benefit analysis...". American Cyanamid, the registrant for Prowl®, alleged that less than complete consideration was given to alternative products and the EPA and USDA were perhaps not aware that Prowl® is an effective alternative for trifluralin. Prowl© and other dinitroanilines were considered by EPA and USDA as effective weed control alternatives for cotton and soybeans. Comparative soybean and cotton yields for other dinitroanilines (Prowl®, fluchloralin, dinitramine, and profluralin) were estimated to provide yields that ranged from 95 to 100 percent of those achieved with trifluralin.

American Cyanamid stated further that the preliminary benefit analysis was in error and outdated. It is true that changes in either the herbicide or agricultural markets would cause the basis for the analysis to imprecisely describe current conditions. However, the Agency maintains that the analysis is still relevant, since minor deviations are normal for an analysis that was never intended to represent any one specific year. The most important issue at hand is whether the relative economic importance of trifluralin, as represented in the August 1978 analysis, is still valid (Gaede, 1980b).

The economic analysis was presented in terms of a "typical" production year for a time period of three to five years following a hypothetical cancellation, taking into account the long-term uncertainty associated with herbicide markets. The Agency was cognizant of limits to the production capacity of other dinitroanilines as well as the uncertainty of when they would become more market competitive with trifluralin.

American Cyanamid indicated that a new production facility would be at full capacity in 1980. In a subsequent communication American Cyanamid stated that the production facility is now fully operational (American Cyanamid Company, 1981). This statement implies that trifluralin's market shares for soybeans and cotton can currently be challenged. While there is some increase in Prowl®'s market shares on both cotton and soybeans, the penetration of these markets is still in the early stages and significant inroads into trifluralin's market share have not occurred (Gaede, 1981). Since Prowl® is priced lower than trifluralin and since the registrant is offering price rebates to farmers, market penetration strategies are at least in the initial stages. Whether there will be high levels of price and other forms of market competition in the future is unknown.

American Cyanamid stated that the Agency's market share estimates of other dinitroanilines were in error. The 10 percent market share estimated by USDA/EPA for other dinitroanilines on soybeans was an accurate estimate of use in 1979 (Gaede, 1980b); though the market share improved in 1980, the previous estimate is probably still reasonable for a "typical" production year.

For the cotton market, the Agency projected an approximate market share of 8.4 percent, a figure which is below the current situation. The ramifications of the low estimate upon the relative economic importance of trifluralin will be shown to be minor in Section III. B. 4.

American Cyanamid [30000/32:#17] also indicated they had pending registrations at that time for Prowl® on potatoes, beans, peas, dry beans, peanuts, and sunflowers. Subsequently registrations were granted for use on potatoes (November 4, 1980), sunflowers (April 9, 1981), and peanuts (April 9, 1981).

Regarding potatoes, 72,000 acres were treated with trifluralin in 1978, amounting to 5.3 percent of the U.S. potato acreage. Benefits were estimated as $387,000 in 1978. Since 5.3 percent is a fairly small percentage, trifluralin would be considered a minor use herbicide for this site. For Prowl®, no data were readily available to assess the current market share. Even if substantial market inroads were achieved by Prowl®, the overall change in the total benefits of trifluralin use would not be of major significance (Gaede, 1981).

Regarding peanuts and sunflowers, 301,000 and 650,000 acres were respectively treated with trifluralin in 1978, amounting to 19.6 percent and 65.0 percent of the total U.S. peanut and sunflower planted acreage. It would be reasonable to expect that the Prowl® market penetration for these two sites (peanuts and sunflowers) would be low, since the product is newly registered (April 9, 1981). Hence, the current overall benefits of trifluralin use would not be expected to change significantly because of these two new registrations. Thus, though Prowl® has three newly registered use sites, the early stages of market development cannot be expected to have much significance upon the overall current benefits of trifluralin use (Gaede, 1981).

The primary contention of American Cyanamid is that the relative economic importance of trifluralin has diminished to such a degree that the Agency should reconsider its regulatory stance. The following paragraphs will provide a qualitative rather than a quantitative assessment of the relative economic importance of trifluralin both in current and future herbicide markets.

4. The Relative Economic Importance of Trifluralin in the Current Soybean/Cotton Herbicide Market

Soybeans - The EPA/USDA estimate of the percentages of planted soybean acres treated with trifluralin has remained relatively stable. However, the number of trifluralin acre treatments has increased by more than 50 percent relative to the August 1, 1978, EPA/USDA "typical" year estimates because of the following factors:

a. The number of soybean planted acres has increased sharply from an average of 52.3 million in the 1974-76 analytical base period to over a total of 70 million in 1979 and 1980 as well.

b. The proportion of soybean acres treated with any herbicide has been increasing over time.

c. Trifluralin's acre treatments of soybeans has expanded since the EPA/USDA analysis was completed.

For all other dinitroaniline herbicides used on soybeans, a 10 percent market share was estimated by EPA and USDA in 1978. Relative to the 1980 soybean herbicide market, this estimate is somewhat low but appears reasonable for a "typical" production year approach (Gaede, 1980b and Gaede, 1981).

In absolute terms, the current economic importance of trifluralin would be accentuated since the number of acre treatments has rapidly escalated relative to the "typical" production year scenario developed in the EPA/USDA analysis.

Cotton - For cotton, the EPA/USDA original estimate of the percent of planted acres treated with trifluralin is approximately 10 percentage points higher than more current estimates. However, the current number of acres treated with trifluralin is nearly identical to the EPA/USDA original estimate of 8.31 million acres (Gaede, 1980b).

Trifluralin's percentage share of the cotton herbicide market has remained relatively stable over the past few years, while the market share of other dinitroanilines has exceeded the 8.4 percent estimated by EPA and USDA. Trifluralin is still by far the leading herbicide used on cotton (over 50 percent of the planted acres) and greatly exceeds the usage of all other dinitroanilines.

The relative market share and economic importance of trifluralin may have diminished slightly when compared to the "typical" year scenario developed in the EPA/USDA analysis (Gaede, 1980b and 1981). However, the total current economic importance of trifluralin to the cotton industry, as indicated by the total number of acre treatments, continues to greatly exceed the other dinitroanilines, though some are as efficaceous.

5. The Relative Economic Importance of Trifluralin in the Future Soybean/Cotton Herbicide Market

In 1978 the future uncertainty of herbicide markets limited the EPA/USDA economic analysis to a "typical" year within three to five years after a hypothetical cancellation. Since future herbicide markets are still highly uncertain, forecasting is not highly precise as estimates are extended further into the future.

However, it would be reasonable to assume (Gaede, 1980b) that trifluralin's future market shares and economic importance to soybeans, cotton, and other crops will diminish to some extent because of the following factors:

a. Alternative weed controls that are cost-effective substitutes will eventually enter the market (e.g., the potential registration of Prowl© for use on beans and peas). It is possible that the market entry of viable alternatives may occur quite rapidly since industry research as well as submissions for registration of other dinitroanilines may have been temporarily kept in abeyance until the EPA regulatory stance on nitrosamines was better understood.

b. Production capacity for other dinitroanilines (e.g., Prowl®) will probably increase, a necessary condition to support a serious market penetration effort by such mechanisms as competitive pricing and rebates. However, given the currently high interest costs for investment capital and inventories, large increases in production capacity and market penetration by competitors may be delayed.

c. In the near future it would also be reasonable to assume that Elanco would attempt to protect its market shares by developing various market strategies (e.g., trifluralin price reductions). Such actions could conceivably improve the overall economic benefits of herbicide use by providing farmers with lower cost weed controls, which may in turn contribute to slightly lower food prices for consumers. It is also possible that Elanco could maintain its market shares for Treflan® (trifluralin) for an extended period of time because of such factors as economies of size in production, patent protection until September, 1985, and strong repurchase intentions of trifluralin users. Sharp declines in Treflan's® market shares are hence difficult to imagine in the near future (Gaede, 1980b).

In summary, the joint EPA/USDA economic analysis completed in August 1978 is deemed adequate to serve as a benchmark for evaluating herbicide market changes or other deviations from a "typical" agricultural production year. The qualitative magnitudes and directions of change in economic impacts of a trifluralin cancellation that have occurred since the EPA/USDA analysis was completed in August 1978 do not justify any change in the Agency's risk/benefit analysis or in its regulatory stance.

C. Comments Relating to Testing Requirements/Regulatory Options

1. Benzimidazole Metabolites of Trifluralin

The Agency was concerned about the exposure of applicators to benzimidazoles (possible metabolites of trifluralin) and therefore proposed in the PD 1/2/3 to require that the registrants perform mutagenicity testing on the benzimidazole metabolites of trifluralin. Nelson et al., (1977) reported the presence of benzimidazole derivatives in the ethylacetate extract of a trifluralin/mammalian hepatic microsome incubation mixture. The SAP, in its preliminary public review of the trifluralin RPAR (SAP, Sept. 20, 1979), indicated uncertainty as to why the Agency required this testing, since the benzimidazoles had not been detected in excretion products of animals during *in vivo* testing.

Elanco [30000/32:#6] also commented that studies on the benzimidazole metabolites would not be relevant since they had only been detected in *in vitro* microsomal studies and not in metabolism studies conducted with trifluralin in mammalian species (goats, rats, dogs). Hence, in Elanco's view, additional mutagenic studies related to trifluralin metabolites are also considered unnecessary.

The Agency has reassessed the in vivo and in vitro studies of trifluralin metabolism (Mauer, 1980). A summary of the in vivo studies follows: Golab et al. (1969) found that about 90 percent of the radioactivity in the feces and urine of a ^{14}C-trifluralin fed goat was concentrated in polar substances located at the origin of TLC (thin layer chromatography) plates. These polar materials were not identified. Since no attempt was made to isolate or identify benzimidazole products in this study, they could have been present. Emmerson and Anderson (1966) reported that about one to three percent of radioactivity in the feces of rats fed radiolabeled trifluralin could be extracted with methanol. Thin layer chromatography of this methanolic extract revealed that the material was associated with polar areas. Thus it is possible, though not established, that the polar material found in the in vivo studies of Emmerson and Anderson (1966) and Golab et al. (1969) contains the benzimidazole precursors 2,3-dihydroxy-2-ethyl-7-nitro-1-propyl-5-(trifluoromethyl) benzimidazoline and/or its dealkylated analog, and 2-ethyl-7-nitro-1-propyl-5-(trifluoromethyl) benzimidazole 3-oxide and/or its dealkylated analog. However, benzimidazole products were not actively looked for in any of the in vivo studies and none were reported. Thus, the available evidence seems to indicate that benzimidazole precursors, but not benzimidazole products themselves, may have been present in trifluralin metabolic products found in urine and feces of rats and a goat (Mittelman, 1980).

The Agency has also reassessed the photodegradation and soil degradation studies. The photodegradation study by Leitis and Crosby (1974) revealed that several benzimidazole products and precursors were produced after irradiation of trifluralin in a methanol solution. Soderquist et al. (1975) found benzimidazole products and precursors after irradiating trifluralin vapor in a photoreactor for to up 12 days. These investigators also collected air samples for seven days after the application of trifluralin to field soil surfaces. On the third day they found concentrations of benzimidazole products at the level of detection, 0.5 ng/m^3. In contrast, about 13.1 ng/m^3 of the precursors were reported on the same day. Since benzimidazole products are photodegradation products of these precursors, it is highly unlikely that any detectable level would be found during application. Therefore exposure of applicators to benzimidazole products would likely be very low. Assuming a concentration of 0.50 ng/m^3 total maximum inhalational exposure to applicators would be about 7.5 ng/person/day (assuming a respiratory rate of 1.8 cubic meters and an eight hour work day).

Therefore, as indicated in the PD 1/2/3 and discussed above, degradation products of trifluralin including some substituted benzimidazoles have been reported to occur in treated soil, as well as under ultra-violet decomposition conditions. There have also been reports of their in vitro occurrence as metabolites of treated rumen microbial cultures (Golab et al., 1969), and as indicated, in liver microsomal preparations from normal and phenobarbital-induced rats (Nelson et al., 1977).

However, when tested in the standard bacterial mutagenicity (Ames) assays, the trifluralin metabolites, including the benzimidazoles previously identified in the in vitro microsomal assay, have proved to be negative in a preliminary report (Nelson, 1978); such tests have previously detected other benzimidazoles (Seiler, 1972). (One measurement in the Nelson, 1978, study was positive, but in a telephone conversation with Dr. Nelson in September, 1980, he indicated it was an erroneous result that was not reproducible in subsequent testing.)

In summary, compared to their unequivocal identification in environmental fate and in vitro studies, the presence of benzimidazole derivatives in mammalian metabolism studies is uncertain. In addition to the major metabolic pathways amply demonstrated for trifluralin in the mammalian studies cited in the PD 1/2/3, that is, by dealkylation and reduction, a large number of polar derivatives with chemical characteristics comparable to benzimidazoles were formed, but not identified (Emmerson et al., 1966). Each one of these represented a minute quantity, and the totality probably represent a minor pathway in the species studied. However, since some of these metabolites could represent the same benzimidazole products previously identified in vitro, the Agency has raised the issue.

On the other hand, unless more definitive, compelling evidence becomes available, the Agency is not prepared to pursue the requirement for additional testing in this regard (Mauer, 1980). Therefore registrants will not be required to perform mutagenicity testing on the benzimidazole metabolites of trifluralin at this time. This represents a change in the Agency's proposed testing requirements outlined in the PD 1/2/3.

2. Reproduction and Teratology

In the PD 1/2/3 the Agency identified areas needing further testing based on an evaluation of reproduction and teratology studies previously submitted by Elanco. While admitting the shortcomings of experimental design which led Agency reviewers to judge the studies unacceptable for regulatory requirements, Elanco [30000/32:#6] contends the studies showed trifluralin had no adverse effects on developmental or reproductive processes of animals when administered at large daily dosages (up to 2000 ppm in the reproduction study; up to 1000 mg/kg in the teratology study), and suggests additional testing may not be necessary.

In its review of the trifluralin RPAR, the SAP was concerned that the reproduction test did not satisfy the testing requirement which was part of its recommended battery to estimate potential risks to man from spindle effects. Hence, the Panel recommended a multigeneration reproductive study modified to include a dominant lethal test.

A newer reproduction study (Elanco, 1977) was submitted to the Agency with the intended purpose of answering some of these questions posed by the SAP in its review of the trifluralin PD 1/2/3. From the findings reported in this study

Elanco suggests that the lack of impairment or modification of reproductive performance in the rat following administration of high dietary levels of technical trifluralin (up to 0.2 percent = 2000 ppm) "...further supports the position that trifluralin does not affect spindle formation in a mammalian system in which there are rapidly developing tissues."

The "newer" study submitted by Elanco is actually a modified one generation rat teratology study performed in 1975, and was designed to satisfy special criteria for Japanese regulatory requirements. Since it is not a multi-generation reproduction study, it does not fulfill the SAP's recommendation (Mauer, 1980). Furthermore, it would not fulfill the sensitivity criterion (power of test) the Agency believes is required for assessing spindle effects, even if modified by inclusion of a dominant lethal test. Finally, at no time were cytogenetic studies performed, specifically, analysis of fetal or maternal tissues for numerical chromosomal aberrations.

The type of testing (a multigeneration reproductive study) which would fulfill the Agency's requirement and which was recommended in the PD 1/2/3 is outlined in the Federal Register published on August 22, 1978 (43 FR 37336).

3. Mutagenicity, Including Heritable Spindle Effects

The Agency proposed in the PD 1/2/3 that registrants would need to perform additional testing of trifluralin for mutagenicity, including heritable spindle effects. Comments included the following.

a. DNA/Gene Effects

Elanco [30000/32:#6] commented that ample mutagenicity studies have already been conducted showing trifluralin is negative for any mutagenic effect, and is not a spindle poison.

Elanco asserts that the Agency's requirement for additional mutagenicity studies is unneccessary since sufficient studies have already been performed, all of which have shown negative results, and hence demonstrate that trifluralin does not interact with genetic material to induce mutagenic effects.

The Agency disagrees with Elanco. Although the Agency has judged that the risks of direct DNA/gene (and chromosomal) effects are low, and mainly associated with the nitrosodipropylamine (NDPA) contaminant of trifluralin products, further tests are required including studies to assess transport to the mammalian gonad (Mauer, 1980). In its review of the Agency's RPAR on Treflan® (SAP, October 9-10, 1979) the SAP agreed with the Agency's position, and suggested these low risks be "verified through properly designed studies on the product as it is currently produced with levels of less than 1 ppm NDPA." (Appendix A, October 15, 1979).

As reviewed in the PD 1/2/3, both the technical grade of trifluralin and various formulations [Treflan®, containing known (up to 177 ppm) or unspecified amounts of the principal contaminant, NDPA] have been reported as negative for direct DNA/gene-chromosome effects in studies involving: bacteria (gene mutation and DNA damage tests); fungi (mitotic recombination); Drosophila (gene mutation and chromosome breakage); and mammalian cells in culture (unscheduled DNA synthesis). Subsequent microbial studies performed in an Agency laboratory, however, have revealed positive results in the Ames Assay as well as in the yeast mitotic recombination test, but at concentrations 2.5 to 9.5 times the highest concentration in previously reported studies (Chen, 1979). Two preparations were tested in the Agency study: A technical grade of trifluralin containing less than 3.0 ppm NDPA; and an NDPA-bolstered technical preparation, to which 100 ppm of the contaminant had been deliberately added. At the dosages used (2400 to 9600 micrograms) both the technical grade chemical and the nitroso-contaminated preparation induced frameshift mutations in *Salmonella* (Ames) strains, but only in the absence of metabolic-activation. When tested in the presence of a metabolic activating system, only the trifluralin preparation with added NDPA was active in the yeast test.

In contrast, NDPA tested by itself has consistently shown positive genetic activity in most of the same *in vitro* tests which have been performed with trifluralin preparations, but only in the presence of metabolic activation. Hence the Agency had concluded that the NDPA contaminant of trifluralin preparations represented a potential risk of direct DNA/gene effects to humans (Mauer, 1980). However, the risk was considered low because of the negative results of trifluralin preparations in the majority of the tests conducted to date, as well as the low potential for human exposure to these products.

On the other hand, information on mammalian *in vivo* testing is lacking and the Agency recommended in the PD 1/2/3 that further testing for both gene mutation and chromosomal breakage be performed in order to better evaluate risk for these genetic effects in mammalian systems. The Agency also recommended studies to assess the potential for trifluralin/NDPA to reach the mammalian germinal tissue in a metabolically active form (Mauer, 1980).

In a continuation of the review of the trifluralin RPAR, the SAP has reiterated its May, 1978, recommendations for a "core" battery of tests selected from the mutagenicity guidelines proposed by the Agency (43 FR 37336, August 22, 1978) for the mutagenicity screening of all pesticides (Appendix A, November 30, 1979). The SAP recommended that the test battery consist of an Ames Assay, (with a dose-response course, if possible), a point mutation assay in mammalian cell cultures (using mouse or hamster cells), and an *in vivo* (mammalian) cytogenetics assay. In addition, the SAP recommended modification of the multi-generation reproduction study to include a dominant lethal test (which would also be required for each pesticide, in addition to the core battery). Finally, it recommended an oncogenicity study in the overall evaluation of mutagenicity.

Using this testing scheme, the Panel concluded that a suitable microbiological test has been performed for trifluralin (Appendix A, November 30, 1979). However, since adequate information from mammalian tests was lacking, the Panel recommended: a gene mutation test in mammalian cells (using Chinese hamster ovary, mouse lymphoma cells, or another validated mammalian cell system), and a cytogenetics assay in mice or rats, examining bone marrow cells, spermatogonia and lymphocytes. If both these assays are negative, the SAP would be satisfied that no significant mutagenic risk is posed by trifluralin, and no further testing should be required.

Thus, the SAP and the Agency are in basic agreement with respect to the requirement for additional testing to assess direct DNA/gene and chromosomal effects in mammalian test systems. However, the Agency differs with the SAP on several minor counts (Mauer, 1980).

First, the Agency is not entirely convinced about the adequacy of the microbial testing of formulated trifluralin preparations. As detailed in the PD 1/2/3, results of tests with the formulations were considered inconclusive since these tests were performed without metabolic activation. In addition, as detailed above, subsequent tests in an Agency laboratory have generated positive results (albeit "weak," in terms of the higher dosages used) in comparable microbial assays using the technical chemical. It is essential that this apparent contradication be resolved by further testing in microbial systems.

Second, while the Agency is satisfied with data indicating that both trifluralin with no detectable NDPA (<1.0 ppm) as well as a Treflan® formulation reported to contain 177 ppm of the contaminant did not induce sex-linked recessive lethal mutations or direct chromosomal damage (dominant lethals, breakage) in Drosophila testing, no comparable germinal tests in mammals are available. Hence the Agency requires performance of an adequate dominant lethal test ("adequate" in the sense of an appropriate number of experimental units per dosage group) in at least one species (mouse or rat) according to standard protocols [43 FR 37336], in addition to the in vitro and somatic mammalian tests. This should be separate from a modified multi-generation study, as the SAP recommended.

Lastly, the Agency cannot agree with the SAP's minimal standard which suggests that if their recommended "core" battery is negative "no significant mutagenic risk is posed by trifluralin and no further tests should be required."

It is the Agency's opinion that appropriate evaluation of trifluralin/NDPA products for potential mutagenic risk to man requires at least two elements (Mauer, 1980): (i) assessment for the presence of active compound in the mammalian gonad [43 FR 37336, Sec. 163.85-1]; and (ii) results from appropriate germinal testing [43 FR 37336, Sec. 163.84-1].

b. Spindle Effects Testing

The SAP commented that: "The best methods for predicting adverse health effects in man from spindle poisons are the multigeneration reproductive test and the dominant lethal test."

In its written review of the trifluralin PD 1/2/3, the SAP agreed with the Agency's position that additional testing for spindle effects be required, especially in mammalian systems (Appendix A, October 15, 1979). The SAP subsequently recommended a sequence of tests which the Panel believes will be capable of estimating risk to man of spindle effects (Appendix A, November 30, 1979).

Specifically, the Panel recommended the following testing scheme, consistent with its previous recommendations on the proposed mutagenicity guidelines (43 FR 37336): a multigeneration reproductive test, modified to provide a statistically significant assay for dominant lethal mutations; if the multigeneration and dominant lethal tests are negative, then a cytogenetics assay should be conducted on the sperm and bone marrow cells of an adequate number of the tested animals used in these or other studies. In the Panel's opinion negative results in these tests would indicate that "no significant risk to man exists from spindle inhibition by trifluralin in normal agricultural use."

In addition to in vivo tests, the Panel also suggested research funding for the development of in vitro assays for spindle effects of pesticides, contaminants and breakdown products (such as an examination of metaphase arrest in mammalian cells), as well as approaches to evaluate the predictability of in vitro tubulin binding of spindle poisons.

Using this testing scheme, the Panel concluded that trifluralin had been inadequately tested for potential spindle effects.

The Agency differs with the SAP in that the Agency does not consider the in vivo tests recommended by the Panel (multigeneration reproductive, dominant lethal and cytogenetics) sufficiently sensitive to adequately assess risk from spindle inhibitors (Mauer, 1980). The Agency does agree, however, with the desirability for the development of sensitive in vivo assays for spindle effects, as well as the funding of research on the predictive value of tubulin binding. The Agency cannot suggest at this time an alternative set of tests since none of the assay systems currently proposed for use in screening programs can unequivocally detect chemicals producing spindle effects significantly relevant to man, such as aneuploidy by nondisjunction or any other mechanisms. The following is a portion of a summary statement by OPP staff scientists delineating the position of the Agency in this regard: (Hill, 1980)

"The Scientific Advisory Panel (SAP) submitted to the Office of Pesticide Programs (OPP) its evaluation of chemicals which may interfere with the cell-division spindle (benomyl, thiophanate-methyl and trifluralin) on November 30, 1979 (Appendix A). The SAP is willing to accept data from a few test systems which are presently available (reproduction and dominant lethal tests plus in vivo cytogenetics) to evaluate safety in regard to spindle effects. Using this scheme the Panel concluded that more testing would be required for trifluralin and that safety had been demonstrated for benomyl and thiophanate-methyl.

"On the one hand, OPP agrees with the Panel that nothing in the review of all the information available on these chemicals, including subchronic toxicity and reproduction studies, indicated significant adverse effects from this toxicity. On the other hand, OPP does not think these systems have the capability to assess fully the degree of hazard from spindle inhibition.

"Basically, OPP staff is of the opinion that there is a lack of information bearing on the sensitivity and adequacy of various tests to evaluate risks from spindle inhibition and, more generally, inhibition of microtubular protein polymerization."

"In addition to in vivo tests, the Panel also suggested research funding for the development of in vitro assays for spindle effects of pesticides, contaminants and breakdown products (such as examining metaphase arrest in mammalian cells), as well as approaches to evaluate the predictability of in vitro tubulin binding of spindle poisons."

"The OPP staff agrees with the SAP as to the need for further investigation on the usefulness of various systems for evaluating risks. To this end, the Agency plans to identify outside scientists who can help us delineate a meaningful research program to fill some of the information gaps and to summarize possible means of risk assessment.

"The problem of assessing risks is heightened when one considers on a broader scale the development of schemes for chemicals which inhibit microtubular polymerization. In this case, one is concerned not only with spindle effects but also all other effects produced by chemicals acting via the molecular mechanism of microtubular inhibition. Since these inhibitors affect all microtubule-related processes, including cell shape, cell movement, intracellular molecular movement, and cellular secretion, many functions may be affected by these 'cellular poisons.' Given these effects, we must decide what are the appropriate toxicological endpoints of concern, how to evaluate them and, lastly, how to evaluate risks. Because of the magnitude of the problem we have decided to start with spindle effects and to enlarge the scope of problems over time."

Therefore, the Agency will not require further tests to assess risks from spindle effects at this time (Mauer, 1980). When appropriate testing is developed, the registrants will be required to perform them to assess effects due to inhibition of spindle fiber formation or function.

4. Labeling Requirements

In the memorandum of October 15, 1979 (Appendix A), the SAP recommended that the Agency adopt Option 3 as detailed in the PD 1/2/3. This option called for the cancellation of all registrations for products containing trifluralin unless registrants modified labeling of their products to reflect less than 1 ppm N-nitroso-dipropylamine (NDPA) contamination.

Elanco has stated that "the proposal to require registrants of trifluralin herbicides to include in the label a statement concerning the level of the NDPA contaminant will not serve to provide meaningful information to users, and therefore should not be adopted. If, however, it is adopted, Elanco urges EPA to postpone implementation until EPA establishes a general policy on nitrosamines in pesticides. The nitrosamine issue is much broader than NDPA in trifluralin. EPA should delay action until development of a policy that would apply uniformly to all registrants of pesticides containing nitrosamines...." [30000/32:#6].

The Agency has reconsidered its proposal to require a statement of the level of NDPA contamination in trifluralin on the product label and has determined that any requirements of this type will not be proposed until Agency policy on this subject is finalized. The Agency therefore withdraws its requirement for trifluralin product label statements on the level of NDPA contamination at this time.

Notwithstanding the foregoing, the Agency will continue to require that the confidential statement of formula for trifluralin containing products be amended to include the level of N-nitroso contamination under the inert ingredients statement.

The Agency initially proposed that this statement should read as follows:

N-nitroso-di-n-propylamine (NDPA)....<1 ppm.

Elanco has provided information on total N-nitrosamine content in more than 600 lots of Treflan® EC; the total N-nitrosamine contamination ranged from <0.01 ppm to 0.96 ppm (Elanco, 1980b).

In view of the risk and exposure analyses discussed in this document which show if the total N-nitrosamine content is kept below 1 ppm, the risk from exposure to the nitrosamine contamination in trifluralin products is negligible, the Agency has determined that in order to assure the public is protected from exposure to nitrosamines, technical trifluralin products may contain no greater than 0.5 ppm total N-nitrosamine contamination.

The Agency will require that the statement in the Confidential Statement of Formula for all technical trifluralin products to be placed under the inert ingredients section shall read as follows:

Total N-nitrosamine contamination .... no greater than 0.5 ppm.

During the formulation of end-use products, some formulators heat the crystalline technical trifluralin to 70°C over several hours in order to liquify it. Because it has been shown by Probst (1981) that NDPA can be generated during heating at 70°C, the limit of total N-nitrosamine contamination in formulated products will be set as a function of the amount of trifluralin in the end-use product with allowance for some nitrosamine generation.

For example, assuming a 0.5 ppm limit in technical product, a 50% formulated product, with no generation of nitrosamines, would be expected to have no greater than 0.25 ppm total N-nitrosamine contamination (0.5 ÷ 2). However, the Agency will allow for a two-fold increase in nitrosamines. Therefore, in a 50% formulated product, the allowable limit would be 0.5 ppm (0.5 ppm in technical trifluralin x 50% trifluralin in the formulated product x 2 to allow for possible nitrosamine generation).

Similarly, a 5% formulated product might be expected, wtih no nitrosamine generation, to have no more than 0.25 ppm total N-nitrosamine contamination (0.5 ÷ 20). However, to allow for twice what would be found in a straight forward dilution, that allowable limit would be 0.05 ppm (0.5 ppm x 5% x 2).

All allowable limits for total N-nitrosamine contamination should be calculated in this same way; i.e., by multiplying 0.5 ppm by the % trifluralin in the formulated product and then multiplying by 2 to allow for possible generation of more nitrosamines during formulation.

Elanco [30000/32:#6] stated that "Once the EPA has established a limit on the level of NDPA contaminant in herbicides containing trifluralin, the requirement must uniformly apply to all registrants of such products." Elanco further stated:

> "The level of NDPA impurity that EPA proposes to establish for trifluralin must apply to all trifluralin registrants and products. There is no justification for EPA to apply a more lenient standard for a producer less capable than the current registrant-producer. The position document suggests, however, that higher NDPA contamination levels may be permitted for new trifluralin pesticide products for which a level of 1 ppm or less cannot be met without substantially increased costs.

> "Establishment of a higher NDPA limit for a new pesticide on this basis would be improper and unjustified. First, Elanco incurred extraordinary costs in achieving consistent NDPA levels of below 1 ppm in trifluralin and it would be arbitrary and unreasonable for EPA to allow other producers to avoid similar costs to achieve similar levels.
>
> "Second, it is well established that the benefits to be taken into account in determining whether a pesticide causes unreasonable adverse effects on the environment include adverse economic implications on agricultural producers and consumers, but do not include production cost impacts on pesticide producers alone. [See FIFRA Section 2(bb); EDF v. EPA, 489 F.2d 1247, 1254 (D.C. Cir. 1973)].
>
> "Finally, in view of the substantial benefits of trifluralin and the conclusion of EPA that a NDPA impurity level of less than 1 ppm is necessary to bring trifluralin into risk-benefit balance, it is inconceivable that a producer of a proposed new pesticide with no established benefits could show that a higher NDPA limit would be appropriate for its pesticide."

Although the Agency does not agree with all of the points in the Elanco argument, it does agree with the Elanco contention that the standard for maximum N-nitrosamine contamination in all trifluralin containing products should be the same. As indicated in its PD 1/2/3, the Agency determined that use of trifluralin contaminated with greater than 1 ppm total N-nitrosamine would be unreasonable because the risks would be increased unnecessarily with no offsetting increase in benefits. Therefore, any future manufacturer of trifluralin containing products will have to achieve a level of no greater than 0.5 ppm of N-nitrosamine contamination in their technical trifluralin products in order too be registered. For formulated products, the level all manufacturers will have to achieve will be calculated on a percentage basis with a built-in factor of two as described above.

IV. Conclusions and Requirements

A comparison of the risks due to exposure to NDPA as set out in the PD 1/2/3 with the maximum risks due to exposure to trifluralin, NDPA, and C_7/C_8 nitrosamines calculated in this document shows that the risks to the general population and workers exposed to Treflan® have not changed significantly. The total dietary risk has increased one order of magnitude from 3.3×10^{-8} to 5.3×10^{-7}. The risk to mixer/applicator/loaders has remained essentially the same and is in the order of 1×10^{-7}. The risk to reentry workers was in the order of 1×10^{-7} due to exposure to NDPA (without taking photodegradation into account) and now is in the order of 1×10^{-9} due to exposure to trifluralin. Thus, the overall risks associated with exposure to Treflan® have not changed appreciably. The source of the risk has changed, but the degree of the risk has not.

Similarly, the benefits derived from the use of trifluralin-containing products have remained relatively constant. At the time of the PD 1/2/3, the economic impact, if trifluralin-containing products had been cancelled, would have been a $300 million loss. There are alternatives for some trifluralin uses as there were then, but trifluralin is still the major herbicide in use for cotton and soybeans, the two most prevalent uses. The qualitative changes in economic impact that have occurred since the EPA/USDA analysis was completed in August, 1978, do not justify any change in the estimate of benefits of trifluralin use.

Therefore, since there is not significant change in risk estimates nor any significant change in benefits,the position presented in the PD 1/2/3 remains unchanged. Based on the best available information, the risks of using trifluralin-containing products are outweighed by the benefits of its use if the registrants meet certain requirements proposed by the Agency.

After reviewing comments from the Secretary of Agriculture, the Scientific Advisory Panel, and others who commented on the Agency's findings and recommendations concerning trifluralin as set forth in Position Document 1/2/3, the Agency has decided to implement the proposed regulatory action (Option 3) as set forth on pages 137-140 of the PD 1/2/3 with a few modifications. A comparison of Option 3 and the regulatory action proposed by this document (PD 4) can be seen in Table 18.

The regulatory action which the Agency will implement is as follows:

The Agency will issue a section 6(b)(1) notice of intent to cancel all technical trifluralin registrations [6/] unless registrants amend the terms and conditions of registration to limit the total N-nitrosamine content in technical trifluralin products to a level not to exceed 0.5 ppm.

[6/] Some registrants have received state registrations for trifluralin to meet special local needs under the authority of 24(c) of FIFRA. These registrations are federal registrations governed by FIFRA. They are subject to the 6(b)(1) notice of intent to conditionally cancel all trifluralin registrations.

Table 18

A Comparison of Proposed Regulatory Actions

Proposal	PD 1/2/3	PD 4
1. Limit N-nitrosamine contamination	NDPA < 1 ppm	Total N-nitrosamine in the technical product, no greater than 0.5 ppm. Total N-nitrosamine in formulated products to be calculated on a percentage basis including a multiplication factor of 2 to allow fo any generation of nitrosamines during formulation.
2. Labeling modification	Required	Require only modification of Confidential Statement of Formula
3. Quality control of N-nitrosamine contamination	Required	Required
4. Mutagenicity testing	Required, including benzimidazole	Required, excluding benzimidazoles
5. Testing for spindle inhibition	Required	Required, but appropriate protocols not yet defined
6. Reproductive effects testing	Required	Required
7. Teratology testing	Required	Required
8. Field monitoring study for ecological effects	Not Required	Required

The Agency will issue a section 6 (B)(1) notice of intent to cancel all formulated trifluralin-containing registrations[6] unless registrants amend the terms and conditions of registration to limit the total N-nitrosamine content in formulated products to a level not to exceed that level which has been calculated on a percentage basis, assuming an upper unit of 0.5 ppm in the technical trifluralin as starting material, including a multiplication factor of 2 to allow for any generation of nitrosamines during formulation.[7]

In regard to those who are currently operating under State-approved trifluralin registrations with Federal trifluralin registration applications pending final EPA decision[8] and those who may have submitted applications for new trifluralin registrations, their applications will be denied unless those applications are amended to satisfy the above requirement. Once these applications are amended to comply with this requirement, the registrations will continue to be reviewed by the Agency to assess whether all registration requirements have been satisfied.

The registrants will be required to comply with this regulatory action 30 days after notification.

A. Amendment to the Confidential Statement of Formula

The Agency will not require that product labeling be modified at this time. However, the amendment to the confidential statement of formula shall appear in that statement under the inert ingredients statement and for technical trifluralin registrations shall read as follows:

Total N-nitrosamine contamination... no greater than 0.5 ppm.

For formulated products containing trifluralin, the statement shall read as follows:

Total N-nitrosamine contamination....no greater than (number to be inserted must be calculated as follows: 0.5 ppm total N-nitrosamine allowed in technical trifluralin x X% trifluralin in formulated product x 2 to allow for possible nitrosamine generation)

These limits are consistent with the PD 1/2/3 where it was determined that the benefits of using trifluralin-containing products outweighed the risks if the level of NDPA was kept below 1 ppm.

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[7] Once registrants have amended the terms and conditions of registration to comply with the maximum total N-nitrosamine contamination requirement, it will be unlawful (under section 12(a)(1)(C) and (E) of FIFRA) to sell or distribute trifluralin products whose registrations have been so amended if they are contaminated with total N-nitrosamine at those levels specified above.

[8] Under 40 CFR 162.17, all state-registered pesticide products, unless governed by section 24(c) of FIFRA, must be registered under FIFRA. Pending a final EPA registration decision, however, state registrants may continue to sell or distribute the pesticide product if solely within intrastate commerce.

In order to maintain consistency in the area of regulation of nitrosamine contamination in trifluralin products, the Agency has determined that all manufacturers of products containing trifluralin will be required to achieve these levels for their technical and formulated products in order to be registered.

Trifluralin registrants will be required to certify that this level is an upper limit in accordance with section 163.61-6 of the Guidelines for Registration of Pesticides in the United States, Subpart D, Chemistry Requirements, as proposed on July 10, 1978 [43 FR 29709-29710]. A person who distributes, sells, offers for sale, holds for sale, ships, delivers for shipment, or receives and (having so received) delivers or offers to deliver a pesticide product, the chemical composition of which differs from the amended chemical composition statement, will be in violation of FIFRA section 12(a)(1)(C) and subject to sanctions under section 13 and 14 of FIFRA.

The registrants of trifluralin must also advise the Agency of the quality control procedures they will institute to assure the Agency that the level of total N-nitrosamine stated in the confidential statement of formula is not exceeded. In addition, registrants must maintain accurate quality control records on these products and make such records available to the Agency on demand.

These requirements apply to all current registrants of trifluralin-containing products and any present or future applicants for registration of trifluralin-containing products.

B. Testing Requirements

The Agency considers the data on the mutagenic potential (including DNA, gene and chromosomal effects) of trifluralin to be inadequate for a precise determination of risk. Additionally, the Agency considers the data on reproduction, teratology, and ecological effects to be inadequate.

FIFRA Section 3(c)(2)(B) states, in part, that:

> "(i) If the Administrator determines that additional data are required to maintain in effect an existing registration of a pesticide, the Administrator shall notify all existing registrants of the pesticide to which the determination relates and provide a list of such registrants to any interested person."

1. Mutagenicity Testing Requirements

Though the Agency will not require testing on benzimidazoles, registrants of products containing trifluralin will be required to test trifluralin and provide the Agency with other data concerning the mutagenic potential of this compound. The registrants will be required to perform further microbialtests and a gene mutation test in mammalian cell cultures,as well as a dominant lethal test, an *in vivo* cytogeneticstest and/or a micronucleus test. When the

Agency identifies, with the help of outside scientists, appropriate tests to assess risks from spindle inhibitors, the registrants willbe required to perform these for trifluralin also. In addition, appropriate evaluation of trifluralin products with NDPA for potential mutagenic risk to man requires an assessment for the presence of active compound in the mammalian gonad as well as appropriate germinal testing.

2. Other Testing Requirements

The Agency will also require the registrants to perform a new multigeneration reproduction test, as well as teratology tests to satisfy data gaps existing for those criteria.

Finally, the Agency has determined that a field monitoring study is necessary to assess possible adverse effects to aquatic organisms in the area of Treflan®-treated fields.

A Notice will be sent, subsequent to the issuance of this position document, to the registrants of trifluralin-containing products informing them of the requirement for performing these tests and describing in more detail the protocols they must follow and the actions they must take to comply with this Notice.

The Agency would like to note that there had been a moratorium on the publication of all decision documents involving pronouncements on products containing nitrosamine contaminants. The Agency lifted the moratorium for this PD 4 because it was unlikely that any changes would be made with respect to the basic decision on trifluralin. Removal of Treflan® products from the moratorium was necessary to expedite publication of this PD 4 to conclude the issue and to remove any impediment the moratorium may have had on the company's marketing and development program.

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